Concerning Newborn Rashes and Developmental Abnormalities: Part II: Congenital Infections, Ichthyosis, Neurocutaneous Disorders, Vascular Malformations, and Midline Lesions

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EDUCATION GAP

Clinicians should be familiar with neonatal skin findings that are associated with systemic disease.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe neonatal cutaneous congenital infections, ichthyosis, neurocutaneous disorders, and vascular malformations and differentiate key features between these abnormalities.
2. Describe symptoms associated with deficiency of interleukin-1 receptor antagonist and its medical treatment with interleukin-1 receptor antagonist.
3. Describe key features of *PIK3CA*-related overgrowth spectrum and its newly approved treatment alpelisib, which inhibits the *PI3K* pathway.
4. List syndromic conditions associated with hemangiomas.

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ABBREVIATIONS

ACC	aplasia cutis congenita
CBC	complete blood count
CIE	congenital ichthyosiform erythroderma
CALMs	café au lait macules
CRS	congenital rubella syndrome
CT	computed tomography
DEB	dystrophic epidermolysis bullosa
DDEB	dominant dystrophic epidermolysis bullosa
EB	epidermolysis bullosa
EBS	epidermolysis bullosa simplex
ED	emergency department
FDA	US Food and Drug Administration
GNAQ	G protein subunit α Q
HSV	neonatal herpes virus
IL-1	interleukin-1
JEB	junctional epidermolysis bullosa
KOH	potassium hydroxide
KTS	Klippel-Trenaunay syndrome
LMs	lymphatic malformations
LUMBAR	Lumbar, Urogenital abnormalities/ulceration, Myelopathy, Bony deformities, Anorectal malformations/arterial anomalies, and Rectal anomalies

INTRODUCTION

Pediatricians should be familiar with neonatal cutaneous manifestations associated with systemic involvement. In this second volume, we review select topics on

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MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
Nd:YAG	neodymium-doped yttrium aluminum garnet
NF1	neurofibromatosis type 1
NLE	neonatal lupus erythematosus
PHACE	Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Cardiac defects, and Eye defects
PELVIS	Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag
PROS	PIK3CA-related overgrowth spectrum
PV	pemphigus vulgaris
PWB	port wine birthmark
SACRAL	Sacral spine/Spinal dysraphism, Anogenital anomalies, Cutaneous anomalies, Renal and urologic anomalies, Angioma of Lumbosacral localization
SCALP	Sebaceous nevus, Central nervous system malformations, Aplasia cutis congenita, Limbal dermoid and Pigmented nevus) syndrome
STS	steroid sulfatase
SWS	Sturge-Weber syndrome
TGM-1	transglutaminase-1
TORCH	toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex
TSC	tuberous sclerosis complex

congenital infections, ichthyosis, vascular malformation, neurocutaneous disorders, blistering disorders, and midline lesions that occur in the newborn period.

CONGENITAL INFECTIONS

In this section, we focus on the cutaneous manifestations of toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex (TORCH) infections and other congenital infections. Generalized erythematous-purpuric macules and papules can be present in most congenital infections. (1)

Congenital Toxoplasmosis

Congenital toxoplasmosis occurs when the mother has been acutely infected with *Toxoplasma gondii* during gestation. (2) The definitive hosts of *T gondii*, a protozoan in contaminated water and food, are cats and other animals included in the feline species. (3)(4) The cutaneous evidence of congenital infection appears as generalized erythematous macules, papules, and purpura. An infant with these skin findings can be described as a "blueberry muffin" baby, a term used for neonates with multiple bluish purplish papules and nodules. These papules and nodules are due to the presence of clusters of extramedullary erythropoiesis or purpura, which can occur in all TORCH infections (most common in rubella and cytomegalovirus). (2) The pathognomonic triad of toxoplasmosis is

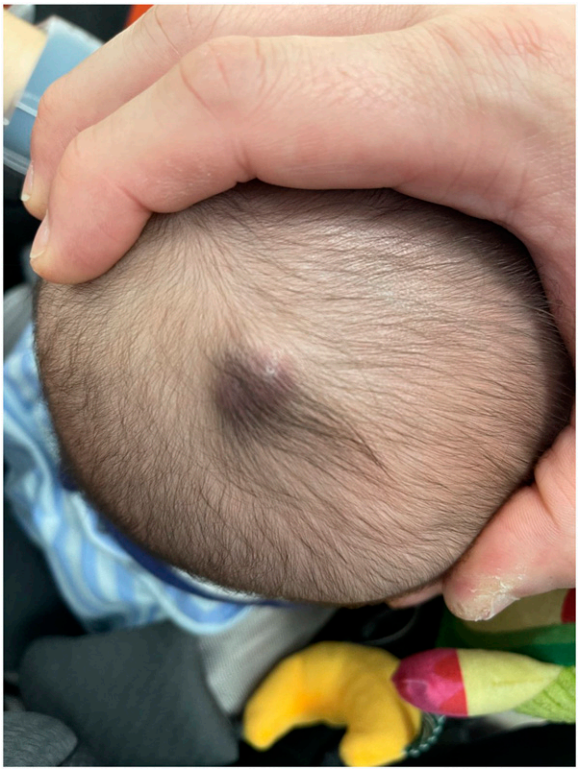

Figure 1. Hair collar sign of aplasia cutis congenita.

microcephalus, chorioretinitis, and intracranial calcifications. (2)(4) Hydrocephalus, hyperbilirubinemia, anemia, thrombocytopenia, and growth restriction can also occur. (2)(4) Ocular signs include chorioretinitis, retinal scars, nystagmus, cataracts, microphthalmia, and blindness. (2) Serial eye examination with complete blood count (CBC) monitoring is warranted. (5) Spiramycin can be started between 7 and 34 weeks of gestation to prevent fetal infection and can be continued until birth. (6) If the fetus is infected or diagnosed after 34 weeks of gestation, treatment should be switched to pyrimethamine, sulfadiazine, and folinic acid. (6)

Congenital Syphilis

Congenital syphilis is caused by the vertical transmission of the spirochete *Treponema pallidum* from mothers infected through sexual contact. (7) Most neonates show no evidence of disease at birth, but manifestations can become evident in the first 3 months after birth. (7) Early congenital syphilis before 2 years of age can present with growth restriction, fever, hepatosplenomegaly, syphilitic rhinitis, and lymphadenopathy. (7) Multiple small, erythematous macules, papules, and sometimes bullae can be present on the lower extremities and soles in early congenital syphilis; skin lesions can also appear as disseminated

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bullae. (7) Late congenital syphilis, occurring after 2 years of age, can present with rhagades (perioral fissures or scarring), granulomas (gummas), and condyloma lata (painless, broad-based, grayish-white to erythematous papules). (7)(8) Congenital syphilis can progress to involve the dental, auditory, musculoskeletal, and central nervous systems. (9) The treatment is with penicillin for 10 days for infants younger than 1 month of age. (1)

Congenital Varicella

Varicella, also known as chicken pox, presents with pruritic friable papules with umbilication and vesicles with erythematous bases in a dermatomal distribution, followed by crusting and desquamation. (10) Skin lesions can heal with scarring in some cases. Varicella skin lesions often begin on the head and trunk and spread to the extremities. (10) In addition to skin manifestations, congenital varicella syndrome can have hypoplasia of the limbs, aplasia cutis (Fig 1), and eye and central nervous system involvement. Varicella has a higher risk of mortality (30% of fatality in the first month after birth) (11) and morbidity to the newborn, especially when the acute maternal infection is acquired perinatally, 5 days before to 2 days after delivery. (12) Postexposure prophylaxis with varicella zoster immune globulin should be considered for neonates with exposure to varicella. Treatment with acyclovir should be started promptly in neonates with severe, disseminated disease and continued for 10 days with close monitoring of liver function and CBC. (11)(12)(13)

Congenital Rubella Syndrome

Congenital rubella commonly presents with a generalized maculopapular erythematous purpuric rash (blueberry muffin rash) consistent with dermal hematopoiesis. (14) Congenital rubella syndrome (CRS) occurs via vertical transmission when an expectant mother is infected with the rubella virus via inhalation of aerosolized particles during the early stages of gestation. (4) Since the introduction of the vaccine, the incidence of congenital rubella has decreased by 99%. (14) The classic triad of clinical manifestations is sensorineural deafness, cataracts, and cardiac defects. (4) CRS is associated with ocular signs, growth restriction, bone disease, hepatosplenomegaly, and thrombocytopenia. (14) Management of CRS is supportive. (15)

Congenital Cytomegalovirus

Congenital cytomegalovirus infection is the leading cause of sensorineural hearing loss in high-income countries and is the most common congenital infection. (16) Congenital cytomegalovirus infection can also present with blueberry muffin rash. (16) Premature infants usually present with hepatitis, pneumonia, blood dyscrasias, and sepsis. (16) Nonspecific signs and symptoms include ocular signs, intracranial calcification, and hepatosplenomegaly. Treatment with valganciclovir for at least 6 months should be started right away. (16)(17) CBC and liver function should be surveilled and serial audiological evaluations should be performed. (16)

Neonatal Herpes Virus

Neonatal herpes virus (HSV) infection can be acquired in-utero, through ruptured amniotic membrane in the setting of maternal viremia; perinatally, through contact with active maternal genital lesions; or postnatally, through contact with a person who has active lesions or who is asymptomatically shedding HSV. (11) Neonatal patients can have cutaneous ulcerations, erosions, and patches; hyperpigmented and hypopigmented macules; crusted papules; and skin contractures from scarring. (18) Long-term sequelae include neurologic, ocular, and otologic manifestations. (18) Women should be counseled regarding antiviral therapy from 36 weeks' gestation until birth if HSV is suspected and should be offered cesarean delivery. (19)(20) Treatment for the neonate is given with intravenous acyclovir for 14 to 21 days with the plan of repeating HSV polymerase chain reaction of the cerebrospinal fluid to guide the additional duration of therapy. (20)

Congenital Candidiasis

Congenital candidiasis is acquired by the newborn while passing through the birth canal or by colonization after birth. (21) The infected newborn may develop generalized papules, pustules, and vesicles, which may slough off to leave large erosive patches and plaques within days after birth. The infected newborn may also present with oral thrush. (21)

When an infant acquires candidiasis at a later time, the dermatitis is usually limited to intertriginous areas of the neck, thighs, and inguinal and anogenital areas and can present as confluent erythema and scaly plaques with associated scattered papules around the main eruption. These scattered papules are called satellite lesions. (22) The risk factors for candidiasis in later infancy include infrequent diaper changing, diarrhea, formula feeding, and recent use of antibiotics. (22)(23)

Potassium hydroxide (KOH) preparations are useful for the identification of the pathogen in skin scrapings, particularly in congenital candidiasis. (24) Oral and cutaneous candidiasis usually respond to nystatin although

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topical antifungals may help. If resistant to the aforementioned therapies, candidiasis can be treated with systemic fluconazole. (24)

Staphylococcal Infections

Staphylococcus has a colonization rate of about 40% in the healthy population, and it is transmitted usually by direct contact. (25) Staphylococcal skin infections of the newborn present as localized vesicles or pustules with honey-colored crusts or extensive exfoliative dermatitis due to profuse peeling of the epidermal layer. (26)(27) Affected neonates can also present with numerous pustular eruptions called staphylococcal pustulosis. (25)

To diagnose staphylococcal infection, a Gram-stain should be performed to detect bacterial infection. To rule out other infectious etiologies, a Tzanck smear can be performed to detect multinucleated giant cells for herpes infection and a 10% KOH mount can be used to detect fungal infections. (28) Also, noninfectious pustular eruptions can be considered for skin scraping examination. (29)

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome, also known as Ritter disease, is caused by bacterial toxins (staphylococcal exfoliative toxin A or B). (30) The exfoliative toxins released by staphylococci bind to a desmosomal adhesion protein, desmoglein-1, causing subcorneal blistering of the epidermis. (30) The diagnosis is made mainly clinically by the presence of tender erythroderma, desquamation particularly at friction zones, perioral crust, absence of mucosal involvement, and a positive Nikolsky sign. The Nikolsky sign is characterized by sloughing of the epidermis or blister formation after lateral or tangential pressure to the skin close to the lesion. Culture may be necessary to decide on antibiotic choice. (30)

ICHTHYOSIS

Ichthyosis is a group of genetic diseases with significant scaling of the skin. Management is aimed at reducing scales, xerosis (dry skin), and skin barrier impairment with the use of antibiotics, emollients, and keratolytic agents such as salicylic acid (though avoided within the first 6 months after birth because of systemic absorption and toxicity). (31) If skin barriers are severely compromised, complications, such as dehydration, sepsis, respiratory distress, and death, can occur. There are various types of ichthyoses, including but not limited to ichthyosis vulgaris, X-linked ichthyosis, congenital ichthyosiform erythroderma, lamellar ichthyosis, epidermolytic hyperkeratosis, and harlequin ichthyosis, in the order of most common to least common. (32)

Ichthyosis Vulgaris

Ichthyosis vulgaris is the most common type of ichthyosis, comprising up to 95% of cases of ichthyosis, with a prevalence of 1 in 100 to 250. (32) Because of mutations in the filaggrin gene, lamellar bilayer maturation is impaired, impacting the lipid distribution of the stratum corneum. (32)(33) Most cases are benign and present with xerosis and diffuse fine scales. Extensor surfaces are more commonly affected, with flexures typically spared. (33) There is a significant association with other atopic disorders. (33) Topical steroids may be used for pruritic areas. (32)

Collodion Baby

Collodion baby is a common presentation of several congenital ichthyoses in which a newborn is encased in a thick, clear, tight membrane that eventually desquamates in 2 to 3 weeks after birth. (34) It is typically inherited in an autosomal recessive pattern and affects about 1 in 300,000 newborns. (34)(35) After desquamation, newborns can have ectropic eyelids and lips. (35) Although 90% of the collodion babies need intervention to prevent long-term complications, ~10% of the babies have normal underlying skin that heals within a few months of life, a condition termed self-healing collodion baby. (36)(37)

Epidermolytic Ichthyosis

Epidermolytic ichthyosis, also known as epidermolytic hyperkeratosis or bullous ichthyosiform erythroderma, is a rare type of ichthyosis that affects 1 in more than 200,000 infants. (38)(39) It results from an autosomal dominant mutation of the keratin 1 and 10 genes. (39) Epidermolytic ichthyosis presents at birth with diffuse erythroderma. Eventually, there is widespread blistering, exfoliation, and erosion, leading to complications. (39)

X-linked Ichthyosis

X-linked ichthyosis, also known as steroid sulfatase (STS) deficiency and X-linked recessive ichthyosis, is the second most common type of ichthyosis. It affects 1 out of 4000 births worldwide. X-linked ichthyosis results from mutations and deletions in the STS gene. Desquamation with larger scales affects primarily the scalp, lower extremities, and extensor surfaces (spares

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flexure surfaces). (40) Associated manifestations include asymptomatic corneal opacities in 50% of male and 25% of female carriers and cryptorchidism in 20% of patients. Systemic retinoids and urea creams have been shown to be effective. (40)

Autosomal Recessive Congenital Ichthyosis

Conditions in this group are (1) lamellar ichthyosis, (2) congenital ichthyosiform erythroderma, and (3) harlequin ichthyosis. The prevalence of these conditions is estimated to be 1 per 300,000 newborns. (41)

Lamellar Ichthyosis

Lamellar ichthyosis is a genodermatosis that is inherited in an autosomal recessive manner. (42) Transglutaminase-1 (*TGM-1*) gene mutations have been known to cause more than 40% of its cases. (42)(43)(44) Lack of *TGM-1* activity leads to defective cornification and desquamation as a result of impaired cross-linking of proteins and lipids. (45) Newborns typically present encased in a collodion membrane. After 2 to 3 weeks, desquamation occurs resulting in diffusely large, thick scales predominantly in the flexural areas, forehead, and lower extremities. (46)

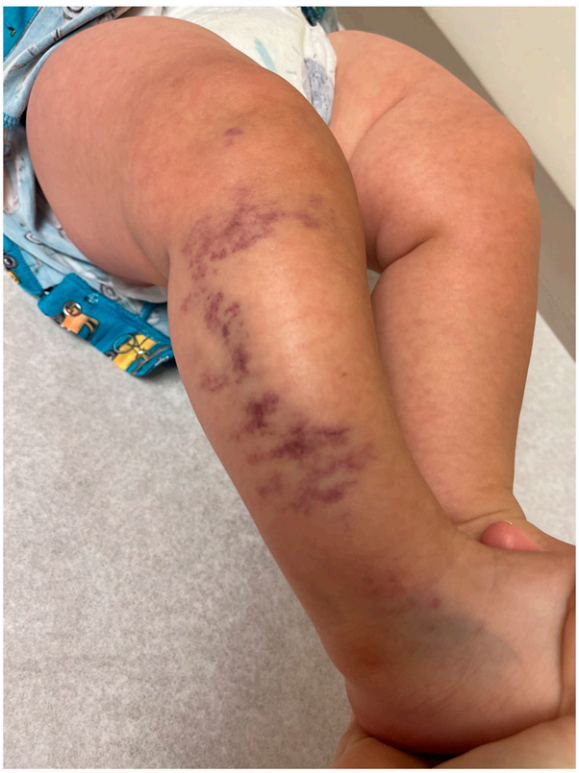

Figure 2. Cutis marmorata telangiectatica congenita.

Congenital Ichthyosiform Erythroderma

Congenital ichthyosiform erythroderma (CIE) is also known as nonbullous congenital erythroderma. (46) CIE is differentiated from other ichthyoses by diffuse erythroderma with overlying fine white scales throughout the body except in the lower limb, in which brown, thick, larger scales can be seen after desquamation of the collodion membrane. (46) Several genes have been implicated in the cause of CIE, including TGM-1, adenosine triphosphate–binding cassette subfamily A member 12, and 4 lipoxygenase 3 genes. Hair and mucosa are typically spared. (47)

Harlequin Ichthyosis

Harlequin ichthyosis is the most severe form of the autosomal recessive congenital ichthyoses. (48) It has been associated with mutations in the adenosine triphosphate–binding cassette subfamily A member 12 gene. This gene is involved in the transport of epidermal lipids and plays a crucial role in skin development. (48) Often born premature, patients present with large, thick plates of skin that resemble armor covering the body. This condition is often fatal within the first few days after birth from complications of a compromised skin barrier. (48)(49)

VASCULAR MALFORMATIONS

Capillary Malformation

Please refer to part I of "Concerning Newborn Rashes and Developmental Abnormalities" for port wine birthmark (PWB), also known as nevus flammeus, and cutis marmorata telangiectatica congenita (Fig 2). Early treatment of PWB (Fig 3A and B) early in life is most likely safe without a need for general anesthesia. In a retrospective analysis, the researchers demonstrated that all of their patients who received pulse dye laser treatment as early as 5 days to 1 year of age had a successful outcome without any safety concerns. (50) Early treatment is paramount since the thin skin thickness in neonates and young infants allows for more efficient penetration of the laser. Therefore, early treatment can prevent progression of PWB to hypertrophy, thick plaques, or nodularity, which can lead to facial disfigurement that can compromise the visual field or feeding depending on the location of the nodules. (50)

VASCULAR TUMORS

Infantile Hemangiomas

Please refer to part I for additional information.

Endothelial glucose transporter protein 1 is a sensitive marker for infantile hemangioma. (51) Although considered benign and typically regresses, the location of an

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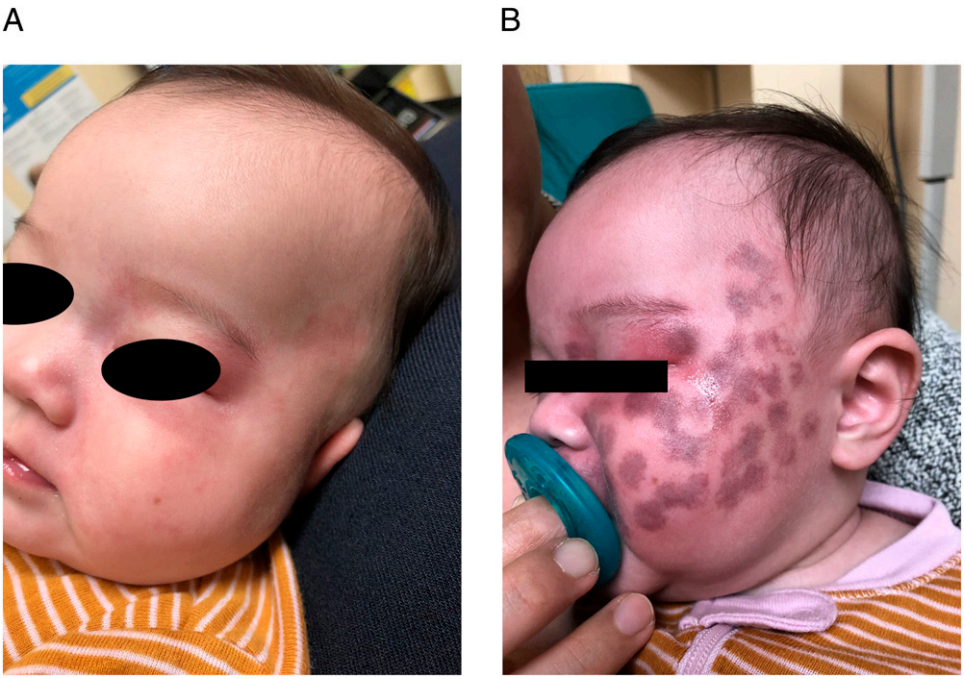

Figure 3. Port wine birthmark on left face before treatment (A), note the purpura right after a pulsed-dye laser treatment, which is the expected end point (B).

infantile hemangioma (Fig 4) may predict complications such as obstruction or interference with vital structures. Also, multiple hemangiomas (≥5) may be an indication of involvement within internal organs, such as the brain, liver, and spleen, and appropriate diagnostic tests should be ordered. (51) The primary form of treatment is the nonselective β-blocker, propranolol. (52) Small superficial infantile hemangiomas may respond well to the use of topical timolol. (52) Infantile hemangiomas presenting in the diaper area and skin creases are susceptible to ulceration and infection; thus, topical and systemic antibiotics, in addition to protective dressings and pastes, may be used. Pulsed-dye laser has also been shown to be effective. Deep and segmental infantile hemangiomas have a longer growth phase and take longer to regress. Scarring, skin sagging, or telangiectasias may remain in up to 50% of children. (53)

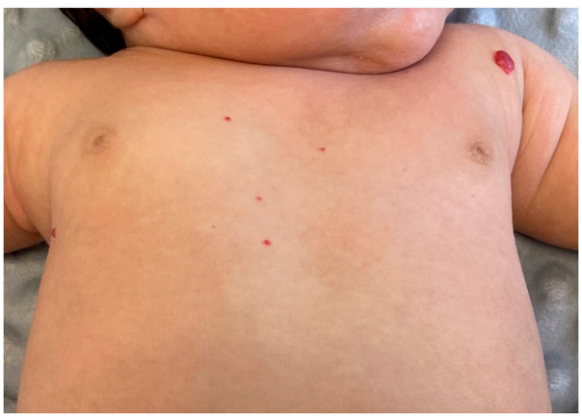

Figure 4. Multiple small infantile hemangiomas on chest.

Congenital Hemangiomas

Congenital hemangiomas (Fig 5) are those that are fully formed at birth and are glucose transporter protein 1–negative unlike infantile hemangiomas. (53) They are subdivided into rapidly involuting congenital hemangiomas, which regress shortly after birth and fully resolve in 12 to 18 months, and noninvoluting congenital hemangiomas that persist indefinitely and do not respond to propranolol. Some authors suggest a third group: partially involuting congenital hemangiomas. (53)(54)

VASCULAR MALFORMATION–ASSOCIATED SYNDROMES

PHACE Syndrome

A small subset of patients with infantile hemangiomas will present with associated anomalies. The presence of a large segmental infantile hemangioma (>5cm) (Fig 6) may be associated with PHACE (Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Cardiac defects, and Eye defects) syndrome. Cerebrovascular anomalies are the most common extracutaneous features observed in PHACE syndrome, followed by cardiac and structural brain anomalies. A multidisciplinary approach with referral to appropriate

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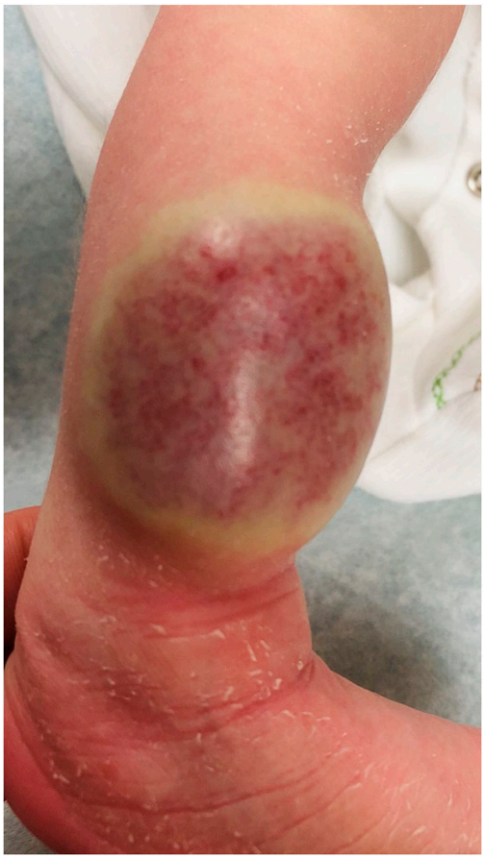

Figure 5. Congenital hemangioma on right lower leg.

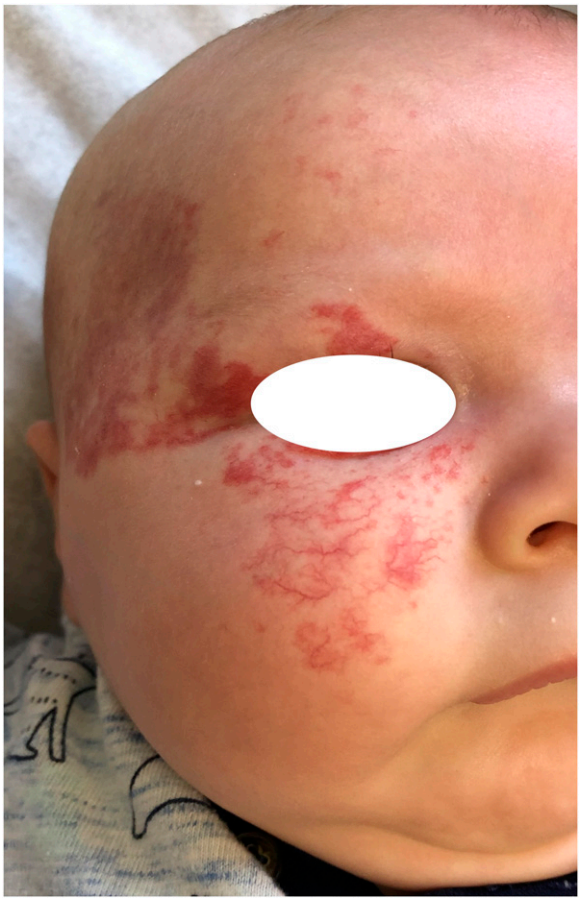

Figure 6. Segmental periocular infantile hemangioma.

specialists would be prudent, along with ordering an echocardiogram and magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head and neck. (55)

Lumbar/Sacral/Pelvis Syndrome

The presence of segmental lumbosacral or anogenital hemangiomas (Fig 7) in association with underlying genitourinary, spinal, and renal anomalies is denoted as LUMBAR, SACRAL, or PELVIS syndrome. (55) These terms are acronyms of associated anomalies. LUMBAR stands for segmental hemangioma of the Lumbar, Urogenital abnormalities/ulceration, Myelopathy, Bony deformities, Anorectal malformations/arterial anomalies, and Rectal anomalies. SACRAL syndrome comprises segmental hemangioma of the Sacral spine/Spinal dysraphism, Anogenital anomalies, Cutaneous anomalies, Renal and urologic anomalies, Angioma of Lumbosacral localization. PELVIS stands for Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag. A spinal MRI is effective in depicting the extent of the anomalies although ultrasound can be considered for a child younger than 6 months of age. (55)

PROS

PROS is a rare group of genetic disorders due to somatic activating mutations of *PIK3CA* with an estimated prevalence of 14 people per million. (56) This gene regulates cell growth and other pathways through phosphoinositide-3 kinases that control cell proliferation, motility, survival, and metabolism. (57) PROS encompasses several disorders with overlapping features of early-onset segmental or focal overgrowth and vascular malformations, such as Klippel-Trenaunay syndrome (KTS), CLOVES, and megalencephaly-capillary malformations. PROS can be divided into syndromic and isolated forms. (58) The criteria for PROS are a somatic *PIK3CA* mutation, congenital or early childhood onset, and 2 of the following: overgrowth of adipose, muscle nerve, or skeletal tissue; vascular malformations (capillary, venous, arteriovenous, or lymphatic); and epidermal nevi. Isolated features that can be seen in PROS (Fig 8) are a large, single lymphatic malformation, macrodactyly,

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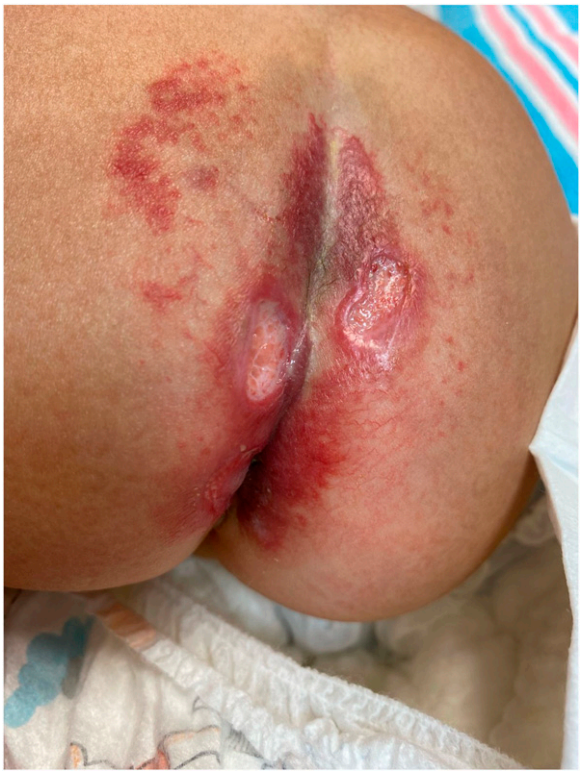

Figure 7. Segmental hemangioma of the sacrum overlying anogenital region.

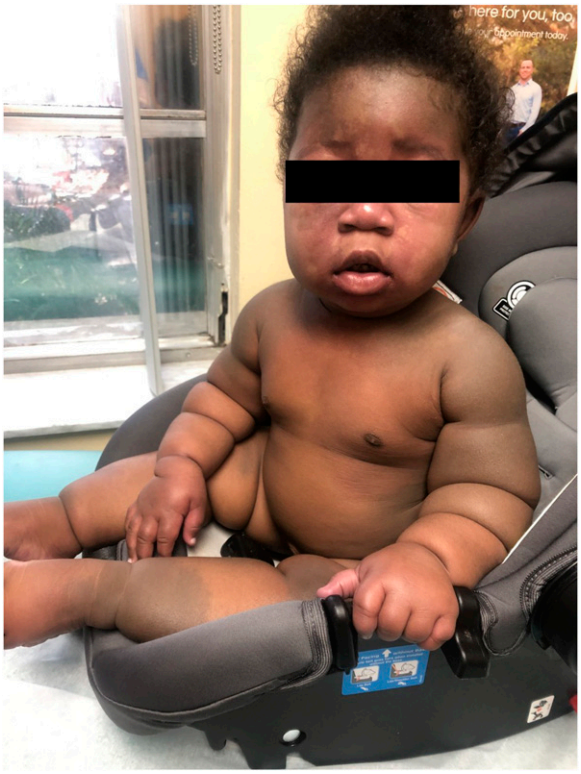

Figure 8. PIK3CA-related overgrowth spectrum with capillary malformation on face and left upper extremity overgrowth.

splayed feet and hands, overgrown limbs, truncal adipose overgrowth, megalencephaly or focal cortical dysplasia, epidermal nevi, seborrheic keratoses, and benign lichenoid keratoses. (59) When confirming the diagnosis, it is important to note that *PIK3CA* mutations are generally undetectable in the blood and are best identified from affected tissue. (58) Disorders in the spectrum are progressive. Targeted therapy with alpelisib, a kinase inhibitor blocking the *PI3K* pathway specifically at the *PI3K* α subunit, was recently approved for adults and for children older than age 2 years with PROS. Clinical trials showed reduction in PROS lesions and improvement in related symptoms. (56)(60)(61)

KTS

KTS (Fig 9) is characterized by a PWB vascular malformation in the form of a combined capillary-venous malformation or capillary-lymphatic-venous malformation and by hemihypertrophy of the affected limb. (62) Vascular malformations are usually present at birth or during early infancy. Superficial veins and venous varicosities are apparent by age 12 years, predisposing patients to thrombophlebitis. (63) A persistent embryonic lateral margin vein, a form of embryologically defective vein with malformation of the vascular trunk, is present in 70% of patients. (64) Geographic capillary malformations are composed of large, well-demarcated, red to violaceous patches with irregular borders favoring the lateral thigh, which may have a lymphatic component. Geographic capillary malformations are associated with a higher risk of complications such as cellulitis. (65) Patients with lighter pink to red blotchy capillary stains instead tend to have a better prognosis. Hypertrophy of the affected limb is characterized by increased length and girth related to soft tissue and fat overgrowth, although bone hypertrophy also occurs. (63) Leg length discrepancy and bony deformities can be progressive and warrant continuing orthopedic care. (66) Malformations of the hands and feet may reflect deep venous system anomalies. (67) Lymphatic disease is common and consists of lymphangiectasia, large lymphatic malformations (LMs), lymphedema, vascular blebs, and pseudoverrucous papules. (68)

KTS is a chronic and progressive condition. A thorough work up starts with genetic analysis for *PIK3CA* mutation. Imaging with duplex ultrasonography, computed tomography (CT) scan, and MRA/MRA is also recommended to evaluate underlying vascular malformations, bone density changes, limb asymmetry, and the extent of musculoskeletal, thoracic, and

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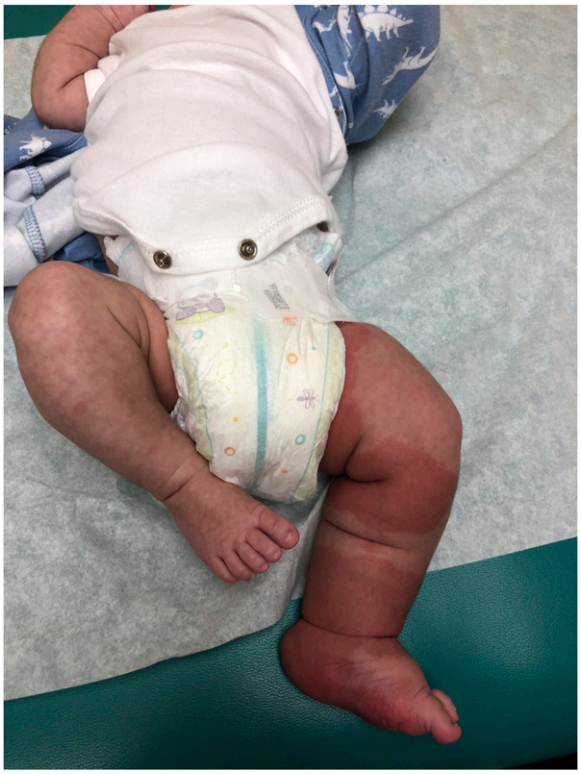

Figure 9. Klippel-Trenaunay syndrome with segmental hemangioma and hemihypertrophy of left lower limb.

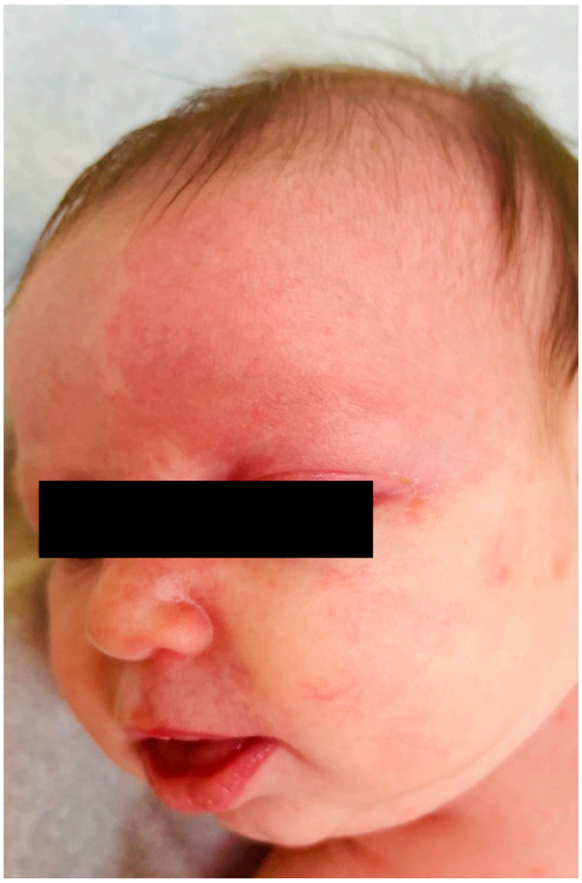

Figure 10. Port wine birthmark of Sturge-Weber Syndrome.

abdominopelvic involvement. (69) Patients with KTS are prone to developing deep vein thrombosis, chronic thromboembolic pulmonary hypertension, and pulmonary embolism. An elevated D-dimer and low fibrinogen levels reflect chronic intravascular coagulopathy due to an abnormal venous network. Prophylactic anticoagulation can be prescribed for those with evidence and risk factors for hypercoagulability. (70) Some suggest periodic echocardiography to assess for pulmonary hypertension. (71) Internal organs and soft tissues can also be affected by vascular malformations that may bleed and lead to anemia. In the case of gastrointestinal bleeding, colonoscopy or capsule endoscopy is warranted and may reveal dilated venous channels. (69) Surgical epiphysiodesis (surgical ablation of a physis to stop its future growth) is indicated for leg length discrepancy, which can exceed 2 cm at skeletal maturity. (68) Pulsed-dye laser is an effective treatment for cutaneous vascular malformations. Sirolimus has been investigated for vascular abnormalities and PROS with some benefit. (59) The most promising treatment option available is targeted therapy with alpelisib, a *PIK3CA* inhibitor, which can reduce PROS lesions. The starting dose is 50 mg daily with food for children age 2 to 18 years and can be gradually increased to 125 mg daily in patients older than age 6 years. Alpelisib major side effects include hyperglycemia, diarrhea, and stomatitis, whereas the more serious risks are pneumonitis and fetal toxicity. (61) Patients should be monitored with CBC and chemistry studies because laboratory abnormalities were reported in patients taking this drug. (61)

Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS) is a rare neurocutaneous syndrome caused by the somatic mutations of the GNAQ (G protein subunit α Q) gene located on chromosome 9q21, leading to capillary venous malformations in the brain and eye. PWB does not cross the midline (Fig 10). Recent studies have revealed that PWB segmental distribution is attributed to embryologic vasculature, not the trigeminal nerve distribution, and that any lesion on the forehead is predictive of underlying SWS warranting further evaluation. (72) The size of the PWB has been associated with severity of neurologic involvement, which may be used as a predictive tool to classify neurologic severity. (73) As a result of intracranial vascular anomalies, SWS can result in cognitive impairments, behavioral

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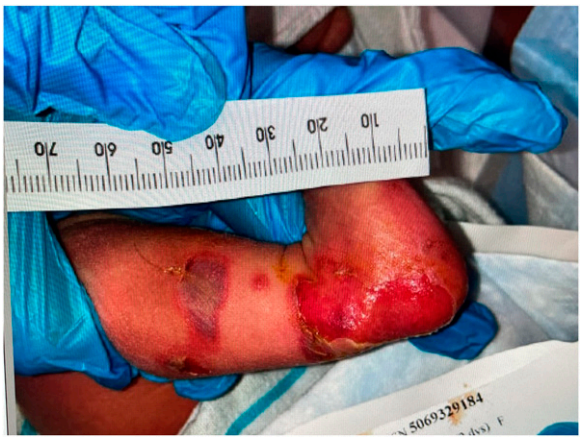

Figure 11. Epidermolysis bullosa (Courtesy of Dr Eduardo Weiss, 2022).

disorders, seizures, headaches, transient focal deficits, and ophthalmic complications. Thus, radiologic imaging with MRI and frequent ophthalmologic examinations are necessary to detect and monitor these abnormalities. (74 Early diagnosis with MRI can be done at the time of first consultation with a confirmatory MRI around the age of 1 year, unless the patient develops neurologic signs that deserve urgent repeat imaging. (75)

Over time, PWB may become hypertrophic and violaceous, and PWB near the eyelid may result in early-onset glaucoma. (76) Hence, early treatment is indicated for lesions close to the eyelid. The treatment of choice is pulsed-dye laser as early as possible. (77) Less commonly in recalcitrant cases, alexandrite or neodymium-doped yttrium aluminum garnet (Nd:YAG) laser can be considered. Novel treatment options, such as angiogenesis inhibitors, are also being explored. (78)

LMs

LMs are rare congenital vascular lesions resulting from the abnormal development of lymphatics, leading to the prevention of drainage into the venous system. (79) The cause of LMs is largely unknown. LMs can be categorized into macrocystic, microcystic, and combined types. Macrocystic LMs are translucent multilocular structures often found in the neck or axilla (referred to as cystic hygromas). Microcystic LMs can be found permeating throughout the dermis as clear firm vesicles; these lesions can involve the oral cavity, throat, tongue, parotid gland, and submandibular gland. Combined lesions contain both macrocystic and microcystic LMs and are commonly found in the trunk and limbs. LMs are persistent throughout life, growing in proportion with the patient without spontaneous involution. Smaller cystic lesions can be excised, whereas sclerotherapy has been used in the treatment of macrocystic LMs; radiofrequency ablation can be used for lesions on the lips and tongue. (79)

BLISTERING NEONATAL DISORDERS

Epidermolysis Bullosa

Epidermolysis bullosa (EB) usually presents at birth or early infancy as vesiculobullous lesions. (10) There are traditionally 3 major inherited forms based on the ultrastructural level in which the cutaneous blister forms: EB simplex, dystrophic EB, and junctional EB. More recently, a fourth form, Kindler syndrome, was added to the classification. (80) The overall incidence of inherited EB across the United States is 19.6 per 1 million live births and the prevalence is 11.1 per 1 million. (80) Biopsies under H&E stain and direct immunofluorescence should be performed to diagnose EB.

EB manifests with fragile skin with atrophic scarring, erosions, and blistering. Supportive therapy is the main goal of management. (80) Saline water cleansing, topical antibiotics, and nonadherent dressings covering the area are indicated, along with avoiding trauma and prevention of wound infection. Potentially lethal complications include intestinal involvement with malabsorption and obstipation, tooth caries and microstomia, osteoporosis and chronic renal failure. (80)

EB Simplex

The incidence of EB simplex (EBS) (Fig 11) is 7.9 out of 1 million live births and the prevalence is 6 in 1 million population. (80) The majority of EBS cases are autosomal dominant mutations within genes that encode structural proteins that reside within the epidermis. The vast majority of EBS cases are the result of mutation within the keratin 5 or 14 genes, the expression of which are in the basal layer of epidermis. There is an autosomal recessive form of EBS, which is due to mutations in the gene encoding a hemidesmosomal protein called plectin and is associated with muscular dystrophy or pyloric atresia. (69)

There are many subtypes of EBS. A localized variant of EBS, previously named Weber-Cockayne syndrome, presents with tense vesicles and bullae usually appearing first on the soles and palms and anywhere on the body exposed to friction. The vesicles and bullae heal without scarring. Histopathology reveals a split above the basal layer of epidermis. (10) A generalized severe subtype of EBS, also known as EBS-Dowling-Meara or EBS herpetiformis, is associated with mutations in the initiation of helix and termination of motifs of keratin 5 and 14. Affected neonates get generalized blisters that form herpetic appearances, as the name suggests. A rare form of EBS with muscular dystrophy has an autosomal recessive defect in the plectin encoding gene. (69)

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Dominant Dystrophic EB

The incidence of dominant dystrophic EB (DDEB) is 2.1 out of 1 million live births and the prevalence is 1.5 out of 1 million population. (80) DEB can have either an autosomal dominant or recessive transmission. DDEB occurs as a result of an autosomal dominant mutation in the type 7 collagen—a substitution of amino acid for glycine in the triple helix of the collagen 7 molecule. (80) Type 7 collagen is the major component of the lamina lucida of the basement membrane zone, an interface that connects epidermis and dermis.

A rare form of DDEB referred to as bullous dermolysis of the newborn is usually confined to the first 1 to 2 years after birth. This is likely due to the temporary disruption in the transport of the type 7 collagen from the keratinocyte cytoplasm to the underlying extracellular matrix. Atrophic scarring, blistering, and milia commonly occur on skin in the patients with DDEB. (80)

Recessive DEB

Recessive DEB is rarer than DDEB. Patients with a severe form of recessive DEB can develop mitten-like deformities of the hands and squamous cell carcinoma. (69)

Junctional EB

The incidence of Junctional EB (JEB) is 2.7 out of 1 million live births and the prevalence is 0.5 out of 1 million population. JEB is mostly transmitted in an autosomal recessive fashion, and most subtypes are associated with mutations in a gene encoding laminin 332, formerly known as Laminin 5, a protein in the lamina lucida of the dermal-epidermal junction. A subtype, JEB with pyloric atresia, is caused by mutations in genes associated with α-6β4 integrin of hemidesmosomes. (69)

JEB-Herlitz type manifests with granulation, blistering, and erosion on the trunk, skin folds, and periorificial and periungual areas. Nail dystrophy is common. (69)

IMMUNOBULLOUS DISORDERS

Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a disease with flaccid bullae and erosions with a median age of onset of 50 to 60 years. Rarely, neonatal PV can be seen in infants of PV mothers, which will present only transiently because of maternal immunoglobulin G crossing the placenta. (81) Skin findings include blisters and mucosal erosions due to circulating anti-desmoglein 3 antibodies. These lesions self-resolve in a few weeks after maternal antibodies are catabolized. (81)

Autoinflammatory: Deficiency of Interleukin-1 Receptor Antagonist

Deficiency of Interleukin-1 Receptor Antagonist is an extremely rare autosomal recessive autoinflammatory syndrome affecting the skin and bone and is thought to be due to mutation in interleukin-1 (IL-1) receptor. Neonates affected with this disease can develop life-threatening systemic inflammation including generalized pustulosis or pustular psoriasis, multifocal aseptic osteomyelitis, periostitis and elevated acute phase reactants within days to weeks of birth. (82) Reportedly about a third of patients are symptomatic at birth. (82) The mortality is 30% in early childhood and no patients have lived through adulthood. Patients tend to respond to recombinant human IL-1 receptor antagonist, anakinra, or longer-acting IL-1 inhibitor, canakinumab. (83)

Autoimmune: Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is an uncommon autoimmune disease that is passed from mother to child through placental transfer of autoantibodies. NLE can manifest as cutaneous lesions, congenital heart block, hepatosplenomegaly and hepatobiliary disease, anemia, leukopenia, thrombocytopenia, and lymphadenopathy. The primary antibodies implicated are anti-Ro/SSA (~95%), anti-La/SSB, or anti-U1RNP. (84) Incidence is estimated to be 1 in every 20,000 births. (85) NLE presents at birth or develops in the first few weeks or months after bith and resolves within 6 to 12 months. Dermatologic examination will typically reveal scaly, pink annular plaques with central scale and telangiectasia; patients may also develop periorbital erythema, sometimes referred to as "raccoon eyes". (86) The rash is often exacerbated by sunlight and is primarily located on the face and scalp but may also affect the trunk, arms, or diaper area. Histologically, the lesions are similar to adult subacute cutaneous lupus erythematosus. Systemic evaluation includes electrocardiography with or without an echocardiogram, a CBC with differential and platelet count, and a hepatic panel. (87) Treatment consists of topical steroids to reduce the risk of scarring and pigmentation; however, lesions usually improve in the months after birth. Patients with severe cases may need systemic therapy or phototherapy. (84) If an infant has severe NLE, mothers may consider hydroxychloroquine for subsequent pregnancies. (87)

NEUROCUTANEOUS DISORDERS

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1), also referred to as Von Recklinghausen disease, has a prevalence of approximately 1:36,000 to 1:40,000 and an incidence rate of approximately from 1:2600 to 1:3000 in the pediatric population. (88) It is an

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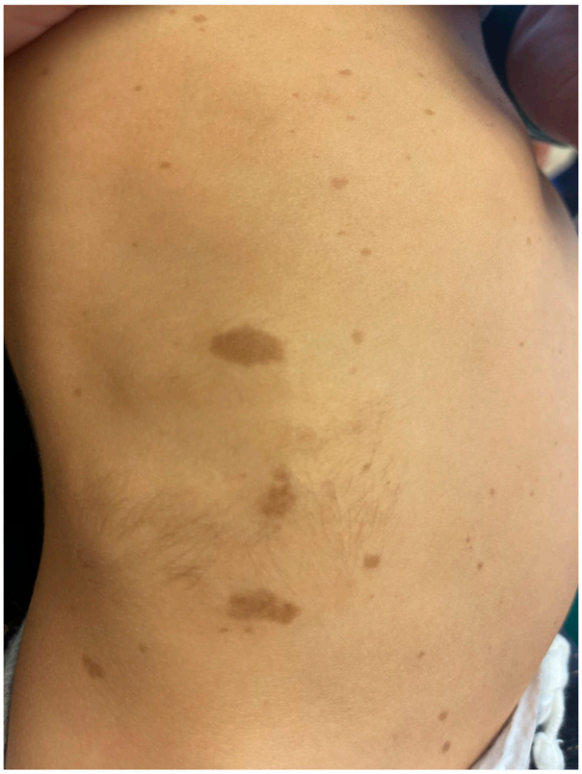

Figure 12. Multiple café-au-lait macules on trunk in neurofibromatosis.

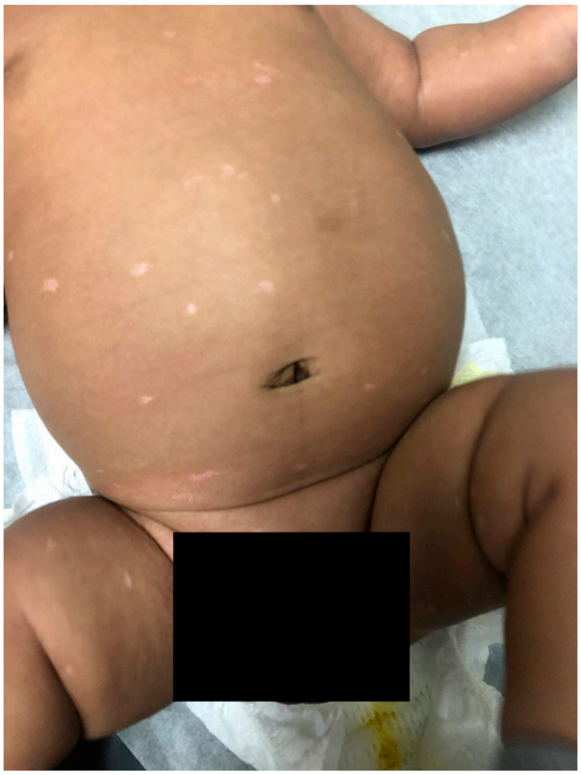

Figure 13. Hypopigmented macules in confetti pattern in tuberous sclerosis.

autosomal dominant, multisystem disorder characterized by a mutation in the *NF1* gene on chromosome 17 that codes for neurofibromin, a protein that regulates cell division in the nervous system. (89) The mutation causes fibrous benign tumors that originate from the central or peripheral nervous system. (90) Clinical characteristics of NF1 are age-dependent; however, ~97% of individuals meet the diagnostic criteria by age 8 years. (91) The most common manifestations affecting greater than 99% of NF1 individuals are cutaneous neurofibromas and café au lait macules (CALMs) (Fig 12). (89) Neurofibromas can occur anywhere on the body and present as pedunculated, firm to rubbery nodules. The presence of 6 or more CALMs, greater than 5 mm prepubertal or greater than 15 mm postpubertal, and more than 2 neurofibromas or 1 plexiform neurofibroma are suggestive diagnostic findings of NF1. (89) An additional diagnostic criterion is freckling in intertriginous and sun-exposed areas, seen in 85% of pediatric patients, particularly axillary freckling, referred to as the "Crowe sign", which occurs at a later age than CALMs but before the appearance of neurofibromas. (89)(92) The ophthalmological finding of 2 or more Lisch nodules is usually seen before age 5 years and with increasing appearance frequency as individuals age. (89) In addition, the presence of an optic glioma; distinctive osseous lesions, such as sphenoid wing dysplasia; or having a first-degree relative with NF1 are all additional diagnostic markers for NF1. (89) Other systemic involvement includes choroidal abnormalities, nonoptic gliomas, seizures, scoliosis, osteoporosis, hypertension, and intellectual disability. (93)

Surgical intervention of tumors may be performed, depending on their proximity to adjacent nerves and risk for damage. Rebound tumor progression occurs in ~44% of initial surgical interventions involving the head and neck when performed before age 10 years. (90) Inoperable plexiform neurofibromas may be treated with selumetinib, an MEK inhibitor that can produce size regression. (94)

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is a rare autosomal dominant, multisystem disorder with mutations in TSC1 on chromosome 9 or TSC2 on chromosome 16, with their protein products being hamartin and tuberin, respectively. (95) Both proteins form a complex to inhibit signal transduction of downstream effectors of the mammalian target of rapamycin (mTOR), thus leading to abnormal regulation of cellular differentiation, proliferation, and migration of affected cell types. (95) The incidence of TSC is ~1:8000 live births. (96) TSC results in hamartomas that

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Figure 14. Giant melanocytic nevus in SCALP syndrome.

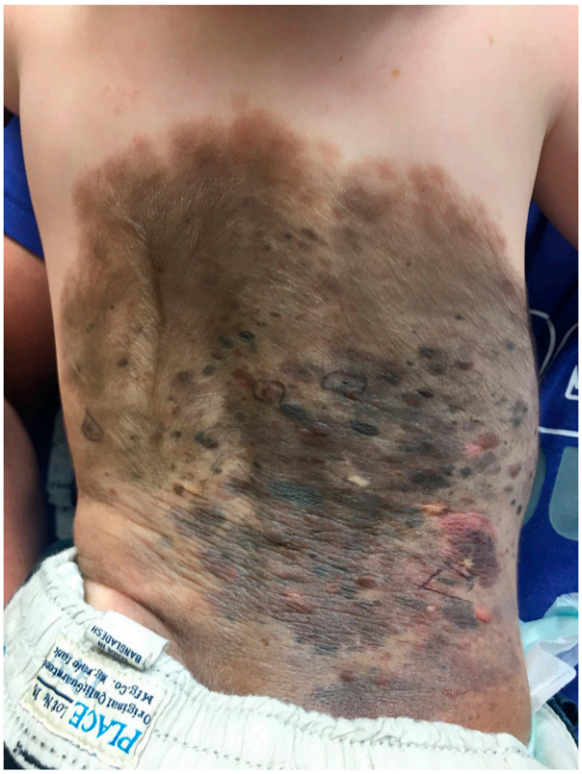

Figure 15. Giant melanocytic nevus in trunk also known as bathing trunk nevus.

can present in the skin, brain, eyes, and kidneys. The pathophysiology of TSC involves a classical triad of mental retardation, seizures, and cutaneous findings, including facial or ungual angiofibromas, shagreen patches, and ash-leaf marks. (69) Around 83% to 90% of Tuberous Sclerosis cases exhibit facial angiofibromas, which typically manifest during the first 10 years of life, typically appearing around the ages of 3 or 4 years. (97) Ash-leaf marks, hypopigmented macules greater than 5 mm with 1 round end and 1 pointed end, appear in 90% of cases, usually at birth or early childhood, and at least half of cases by age 2 years; in fewer cases, approximately 2% to 20%, "confetti lesions," which are hypopigmented 1- to 3-mm macules, may present throughout the trunk or extremities (Fig 13). (97)(98) Shagreen patches, a connective tissue hamartoma with a fibrous texture and peau d'orange appearance, usually present on the lumbosacral region within the first decade after birth in nearly 50% of cases. (98)

Facial angiofibromas can be treated with topical mTOR inhibitors, like rapamycin, or with pulsed-dye laser (enhanced with 5-aminolevulinic acid), ablative laser, and surgical excision; in the case of ungual angiofibromas, a carbon dioxide laser may be used for lesions not fit for surgical excision. (98)(99)

A recently approved treatment for facial angiofibromas is sirolimus 0.2% topical gel, for children age 6 years or older. (100) TSC-associated seizures, subependymal giant cell astrocytomas, and renal angiomyolipomas can be treated with everolimus, which is considered a multisystemic therapy (currently approved for age 2 years and older). (101)

SCALP Syndrome

SCALP (**S**ebaceous nevus, **C**entral nervous system malformations, **A**plasia cutis congenita [ACC], **L**imbal dermoid and **P**igmented [giant melanocytic] nevus) syndrome is a rare, congenital neurocutaneous condition (Fig 14). The etiology is unknown but believed to have a genetic basis, in particular, to the NRAS pathway. SCALP syndrome shares some similarities to nevus sebaceous syndrome but has additional features. (102) Sebaceous nevi are typically on the head and neck and ACC is seen on the scalp or nearby. Multiple giant melanocytic nevi (Fig 15) can be present and limbal dermoids affect 1 or both eyes. Patients may experience seizures and developmental delay due to cerebral or ventricular malformations or neurocutaneous melanosis. (103) Work-up includes CT scan and MRI of the head and electroencephalography if indicated.

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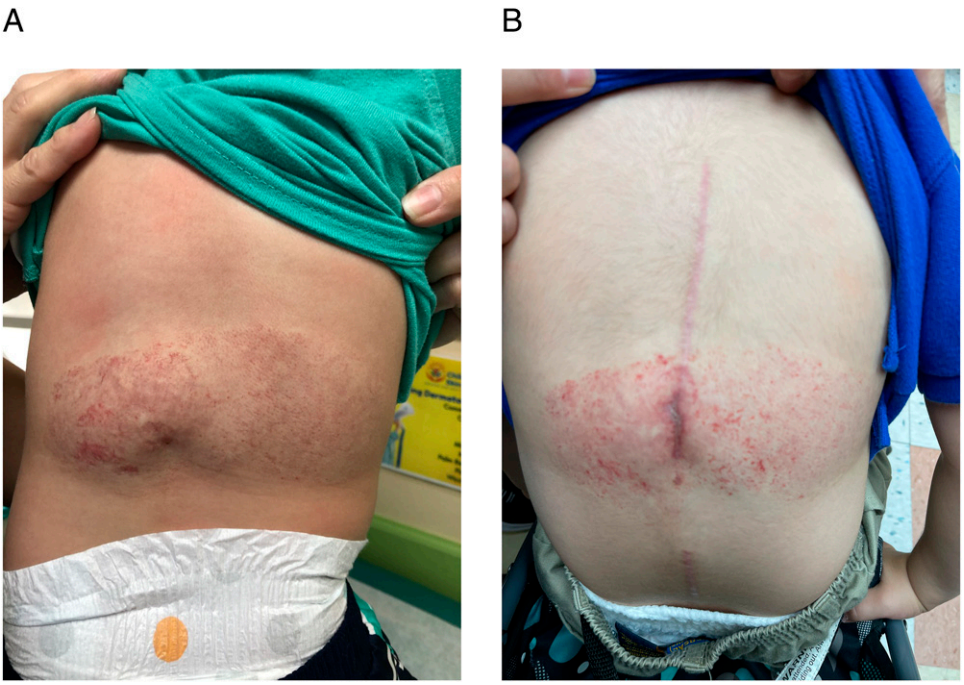

Figure 16. Tethered cord with dimple. A. Before surgery. B. Status postneurosurgical correction on right.

Treatment is tailored to each patient on the basis of presentation, with multidisciplinary surgical and medical management. (103)

MIDLINE LESIONS

Encephalocele

An encephalocele is a neural tube defect in which there is a bony defect in the skull leading to herniation of the brain, meninges, and cerebrospinal fluid outwards into a sac-like protrusion. (104) Although there are multiple theories as to the etiology of this defect, one of the most accepted is that it is secondary to the lack of separation of ectoderm from neuroectoderm after the neural folds close. Some cases have also been linked to TORCH infections. (104) The incidence of encephaloceles is ~1 in 10,000 births, and it is more common in female neonates. (104) An encephalocele presents as a soft, bluish mass with overlying normal skin or a thin, glistening membrane that can be pulsatile and apparent with the Valsalva maneuver or with crying. Encephaloceles vary in size and occur in the midline or the paramedian (primarily on the occiput or vertex), extranasal, intranasal, or pharyngeal areas. (105) Skin ulceration is a potential complication. The defect is usually detected with prenatal ultrasound, but a postnatal MRI is the imaging modality of choice because it will better evaluate any accompanying abnormalities of the brain and of the tissue within the encephalocele. The treatment is surgical. (105)

Spinal Dysraphism

Spinal dysraphism comprises a group of congenital abnormalities in the bony formation of the spine or spinal cord. This group ranges from meningocele and myelomeningocele (spina bifida aperta) to open spinal dysraphism with exposed neural tissue or occult spinal dysraphism with skin-covered abnormalities, such as a tethered cord. Spinal dysraphism is thought to be secondary to the abnormal growth and development of the neuroectoderm, mesoderm, and ectoderm, usually because of multiple factors, including deficiency in perinatal folic acid intake required of neural tube development. Incidence is between 0.5 and 8 in every 1,000 births. (106) The literature suggests that more than 80% of children with midline cutaneous lesions in the lower back have tethered cord syndrome. Tethered cord (Fig 16A and Fig 16B) is usually located in the midline of the lower back, and tethered cord syndrome is associated with hypertrichosis, hemangiomas, lipomas, or dimples. (105) If a dimple lies above the gluteal cleft and is greater than 5 mm, an underlying spinal anomaly is suspected. (105) Patients with dermal sinus and diastematomyelia can be seen with occult dysraphism; some can develop meningitis. If one suspects occult spinal dysraphism, imaging with a spinal ultrasound is recommended within the first 2 to 3 months after birth, followed by MRI if needed. Because of the ossifying of the spinal processes, it is challenging to ultrasound image the spinal cord after 3 months of age.

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Imagining studies include lumbar radiographs, CT scan of the brain and spinal cord, and MRI (gold standard). Treatment is usually surgical. (107)

Summary

- TORCH infections can present as a generalized maculopapular erythematous purpuric rash, commonly known as blueberry muffin rash. (1)(2)(3)(4)(7)(10)(11)(12)(13)(16)(17)(18)(19)(21) (Based on observational reports [large case series and case reports] and consensus)
- X-linked ichthyosis, also known as steroid sulfatase deficiency, manifests with scales predominantly in the scalp, lower extremities, and extensors, whereas lamellar ichthyosis involves flexural areas, along with forehead and lower extremities. (40)(46) (Based on consensus)
- The location of hemangiomas can determine the presence and severity of complications. PHACE, PELVIS, LUMBAR, and SACRAL are syndromic conditions with the common finding of hemangiomas. (55) (Based on evidence as well as consensus)
- Spinal MRIs are the imaging method of choice to detect anomalies related to LUMBAR/SACRAL/PELVIS syndrome; ultrasonographies are also acceptable for those younger than 6 months of age. (55) (Based on consensus)
- The PROS of diseases is due to a somatic activating mutation and has early onset of vascular malformations; focal overgrowth of adipose, nerve or musculoskeletal tissue; and epidermal lesions. (58) (Based on expert consensus.) A novel medication alpelisib, a *PIK3CA* inhibitor, has been approved for treatment of PROS. (56)(60)(61) (Based on evidence from clinical trials)
- KTS is part of the PROS and presents with limb hemihypertrophy and both superficial and deep vascular malformations. Management may require a multidisciplinary approach, imaging studies of affected areas, anticoagulation, and treatment with alpelisib. (61)(62)(69) (Based on current evidence)
- The size of the facial PWB can be used as a predictor of neurologic severity in SWS. (76) (Based on strong evidence.) PWB should be treated with pulsed-dye laser as early as possible. (74) (Based on research evidence and consensus)
- Sclerotherapy and ablation are the treatment options for LM since spontaneous regression is not frequent. (79) (Based on research and consensus)
- NLE usually presents at birth and resolves between 6 and 12 months of age, (86) and evaluation should include electrocardiography with or without echocardiogram. (84–87) (Based on current literature)
- EB manifests with fragile skin with atrophic scarring, erosions, and blistering, and the standard of care involves avoiding trauma, preventing wound infection, and providing supportive care. (80) (Based on expert consensus)
- Neonatal pemphigus vulgaris will present only transiently because of maternal immunoglobulin G crossing the placenta. (52) Skin findings of blisters and mucosal erosions seen in patients with neonatal pemphigus vulgaris will self-resolve in a few weeks after maternal antibodies are catabolized. (81) (Based on expert consensus)
- Patients affected with deficiency of interleukin-1 receptor antagonist develop life-threatening systemic inflammation, including generalized pustulosis similar to pustular psoriasis, multifocal aseptic osteomyelitis, periostitis, and elevated acute-phase reactants and tend to respond to recombinant human IL-1 receptor antagonist, anakinra, or longer-acting IL-1 inhibitor, canakinumab. (83) (Based on expert consensus and observational reports)
- Pediatric patients with neurofibromatosis I present with Crowe sign, also known as axillary freckling. Axillary freckling may often appear after the onset of CALMs but before the presence of neurofibromas. (89,92) (Based on evidence and consensus)
- TSC is associated with a classic triad of mental retardation, seizures, and cutaneous findings of facial or ungual angiofibromas, Shagreen patches, and ash-leaf marks. (69) (Based on consensus)
- Sirolimus, an mTOR inhibitor, has been FDA (US Food and Drug Administration) approved for the treatment of facial angiofibromas in ages 6 years and older when administered as a 0.2% topical gel formula. (95)(100) (Based on evidence from clinical studies and consensus)
- Everolimus, an mTOR inhibitor, has been approved as an adjunctive therapy for TSC-associated seizures, subependymal giant cell astrocytomas, and renal

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angiomyolipomas. (101) (Based on evidence from clinical studies and consensus)

- SCALP syndrome is a rare condition presenting with a sebaceous nevus, central nervous system malformations, ACC, limbal dermoid and pigmented (giant melanocytic) nevus. (102)(103) (Based on current literature)
- Prenatal ultrasonography or postnatal MRIs are the imaging modalities of choice for diagnosing encephaloceles. Skin ulceration is a potential complication. (105) (Based on consensus)
- Tethered cord is a known complication and should be evaluated for in patients with spinal dysgraphism. (105) (Based on consensus)
- Regarding spinal dysraphism, imaging with spinal ultrasonography is recommended in the first 2 to 3 months after birth, followed by MRI if needed. (107) (Based on current evidence)

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2022-005640.

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PIR QUIZ

This longer quiz will be worth 1.5 AMA PRA Category 1 Credit™, to reflect the length of time expected to learn. Because there are only 2 quizzes in this issue, claiming ABP MOC Part 2 points will not be possible until November 2023 instead of October 2023. Before a 2023 MOC Part 2 claim can be processed, 30 total PIR quizzes must be completed.

1. A newborn infant is born at 37 weeks' gestation to a 30-year-old G2P1 woman who is HIV negative, group-B streptococcus negative, and rubella-immune who received routine prenatal care. The baby is noted to be small for gestational age, diagnosed with intrauterine growth retardation, and has intracranial calcifications seen on a prenatal ultrasound. At birth, he is noted to have multiple bluish purplish papules and nodules consistent with a "blueberry muffin" rash. Abdominal examination reveals hepatosplenomegaly. There is no evidence of cataracts. The baby fails the initial hearing test performed at birth and is diagnosed with sensorineural hearing loss. Congenital infection with which of the following causative agents is the most likely cause of this patient's symptoms?

   A. Cytomegalovirus.
   B. Herpes simplex.
   C. Rubella.
   D. *Toxoplasma gondii.*
   E. *Treponema pallidum.*

2. A 3-year-old girl is brought to the emergency department with a 1-day history of fever, chills, and a blistering rash over pressure areas of her body. The parents report that her rash starts as painful, reddish blotches that progress to blisters, some of which result in sloughing of the skin. These blisters appear over friction zones. On physical examination, there are multiple painful desquamated areas, with some intact blisters seen over her upper and lower extremities. There is perioral crusting but no involvement of her eyes or oral mucosa. She is otherwise healthy and receives no medication. Which of the following best describes the pathophysiologic mechanism responsible for this patient's blistering condition?

   A. Bacterial toxins.
   B. Genetic mutation in filaggrin gene.
   C. Genetic mutation in transglutaminase-1 gene.
   D. Localized viral multiplication.
   E. Steroid sulfatase deficiency.

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3. A 3-week-old male infant is brought to the clinic by his parents for follow-up. Ten days prior, he presented with dry skin and scaling for which he was prescribed emollients and moisturizers, his family was advised to use mild soap and laundry detergent, and genetic tests were ordered. Today, the parents report that the baby continues to have significant scaling of the skin, most prominently over the extensor surfaces despite the use of moisturizers and emollients. Genetic tests reveal a mutation in the filaggrin gene, which results in impaired lamellar bilayer maturation impacting the lipid distribution of the stratum corneum. The study results are consistent with which of the following diagnoses in this patient?

    A. Collodion baby.
    B. Epidermolytic ichthyosis.
    C. Harlequin ichthyosis.
    D. Ichthyosis vulgaris.
    E. X-linked ichthyosis.

4. After discussing with the parents the possible diagnosis in the patient in the vignette in question #3, the parents are concerned that the baby seems irritable, moving his extremities as if he is feeling itchy. In addition to continuing emollients and moisturizers, which of the following is the most appropriate next step in treatment?

    A. Topical salicylic acid.
    B. Topical steroids.
    C. Topical urea cream.
    D. Systemic antihistamines.
    E. Systemic retinoids.

5. A newborn male infant is born at term via spontaneous vaginal delivery with no perinatal complications. Shortly after birth, the baby was noted to have vesiculobullous lesions. The clinician suspects epidermolysis bullosa (EB) and studies are ordered. The work-up should include which of the following studies to confirm the diagnosis of EB?

    A. Bacterial culture of skin scrapings.
    B. Genetic analysis for *PIK3CA* mutation.
    C. Potassium hydroxide preparation of skin scrapings.
    D. Skin biopsy under H&E stain and direct immunofluorescence.
    E. Tzanck smear from the one of the vesiculobullous lesions.

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6. A 25-year-old woman G1P0, with history of systemic lupus erythematosus, delivers a term female newborn via spontaneous vaginal delivery. The baby cried immediately at birth and was noted on initial physical examination of the skin to have scaly pink annular plaques with central scale and telangiectasia over the face, scalp, and diaper area. In this patient, it is important to monitor for which of the following complications?

   A. Angiofibromas.
   B. Deep vein thrombosis.
   C. Heart block.
   D. Leukocytosis.
   E. Pulmonary hypertension.

7. An 18-month-old boy with a history of developmental delay was found by his mother in bed having what looked like a seizure. The mother called 911, and the patient was brought to the emergency department (ED) by paramedics. The patient has no fever, congestion, vomiting, or diarrhea and is on no medications. On arrival at the ED, the child is sleepy but arousable. Physical examination reveals 2 elliptical hypomelanotic macules over the trunk, which are better seen with a Wood lamp. The patient is admitted to the hospital for further evaluation. The suspected diagnosis in this patient is associated with other clinical characteristics, some of which are expected to be seen later in life. Which of the following is not part of the clinical picture that is expected to be seen in this condition?

   A. Autosomal dominant inheritance with mutations on chromosomes 9 or 16.
   B. Axillary freckling.
   C. Connective tissue hamartoma with a fibrous texture.
   D. Facial angiofibromas.
   E. Hamartomas in the skin, brain, eyes, and kidneys.

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