Connecting the Spots: Hyperpigmented Lesions in Children

ABSTRACT

Hyperpigmented lesions are common in the pediatric population and identifying their etiologies can be challenging for physicians. Patients and caregivers may worry that hyperpigmented lesions are dangerous, associated with an internal illness or that they may lead to skin cancers. Having a better understanding of the causes and natural histories of these lesions may help to guide management and alleviate worry. This review article will provide an overview of select common and uncommon causes of hyperpigmented skin lesions in children.

Congenital

COMMON

- Café-au-lait spot
- Congenital Nevi
- Epidermal Nevi

UNCOMMON

- Incontinentia pigmenti
- Xeroderma Pigmentosum
- Segmental pigmentation disorder
- Congenital Smooth Muscle Hamartoma
- Plexiform Neurofibroma

Acquired

COMMON

- Post-inflammatory hyper-pigmentation
- Freckle (Ephelide)
- Acanthosis nigricans
- Fixed Drug Eruption
- Terra firma-forme dermatosis

UNCOMMON

- Phytophotodermatitis

KEYWORDS: hyperpigmentation, pediatric

ABOUT THE AUTHORS

Lisa M. Flegel, *Medical Degree Undergraduate Program, Northern Medical Program, University of British Columbia, BC.*
Joseph M. Lam, MD, FRCPC, *Clinical Assistant Professor, Department of Pediatrics and Dermatology, University of British Columbia, BC.*

Introduction

Skin pigmentation is determined by the pigment melanin, which serves to protect the body from ultraviolet (UV) radiation. Melanin is produced by melanocytes, stored in melanosomes and then transferred to keratinocytes. Skin will appear darker when there is more melanin, a larger number and size of melanosomes, and a slower rate of degradation of melanosomes.

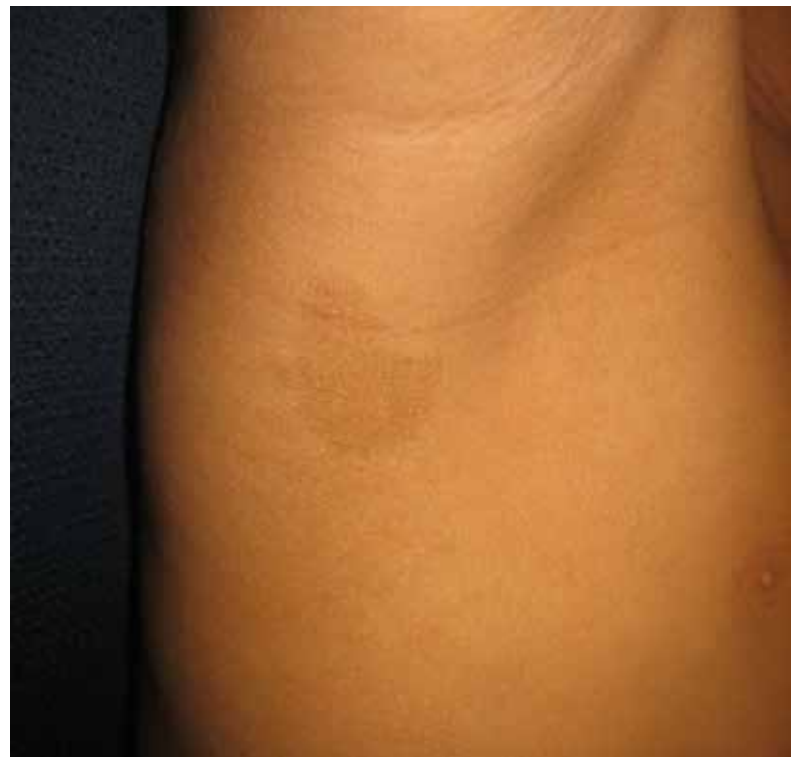
The mechanism of skin darkening can be triggered by exposure to UV radiation, which stimulates the production of melanin. Inflammation can also produce hyperpigmentation through a breakdown in the skin barrier which allows deposits of melanin to accumulate in the dermis. Certain congenital conditions can result in aberrant production of melanin, or an increase in the size and number of melanosomes. As well, hyperkeratosis can make the skin appear darker by an increase in the number of keratinocytes, not by an increase in pigment.

COMMON CONDITIONS

Café-au-lait Spots

Café-au-lait spots, or CALS, are well-circumscribed, oval or round, hairless macules or patches that can be tan to dark brown in color (Figure 1).[1] They can be seen at birth or develop shortly after. CALS have a wide variety of sizes and can

Figure 1: Café-au-lait Spots



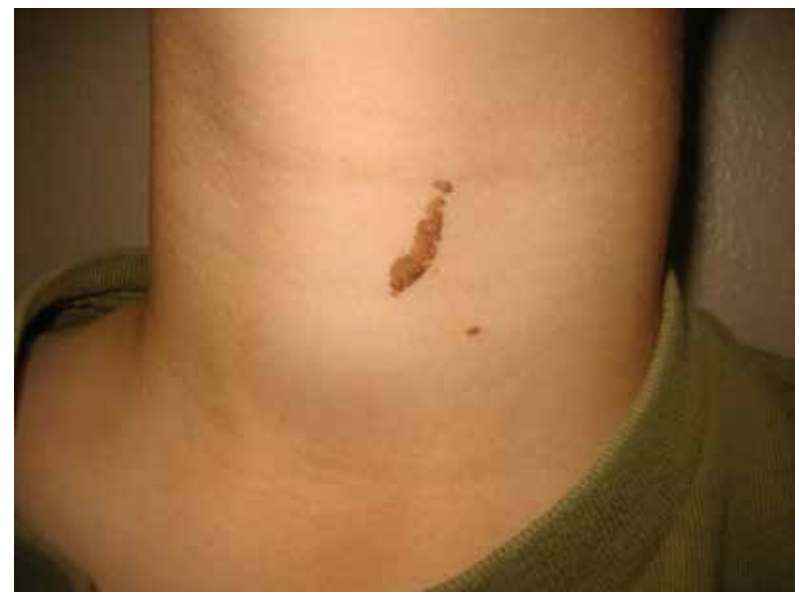
range from smaller lesions of a few centimeters to much larger lesions. Treatment of CALS is not necessary unless for cosmetic purposes. Topical depigmentation therapies have not proven successful in the long-term and repigmentation can occur.[1] Up to 33% of children have one or more CALS and most have no associated disease.[2] Having six or more CALS can be associated with conditions such as neurofibromatosis type 1 and Legius Syndrome.[1] Rarely, CALS can be the sign of diseases such as McCune-Albright syndrome, Fanconi anemia, Russell-Silver syndrome, LEOPARD syndrome, Cowden syndrome and Banayan-Riley-Ruvalcalba syndrome.[3]

Epidermal Nevi

Epidermal Nevi (EN) are benign congenital lesions caused by hyper-

plasia of structures in the epidermis. Most EN are noticed at birth or in early childhood. They appear as tan or brown papules or plaques with a velvety or verrucous texture (Figure 2). They can be composed of single or multiple lesions and typically follow the Blaschko lines, the pattern on the skin which reflects the route of migration of epidermal cells during fetal development. The most common location is on the head and neck, followed by the trunk and proximal extremities.[4] Treatment of EN is not medically necessary but patients may want these lesions removed for cosmetic purposes. Superficially destructive therapies, such as cryotherapy, laser ablation, electrodessication, dermabrasion, and topical retinoids, are generally not successful as the lesions tend to recur.[2] Definitive removal may be achieved by complete surgical excision but this will result in a residual scar. Treatment is usually individualized with surgery generally reserved for single or small lesions.[2]

Figure 2: Epidermal Nevus

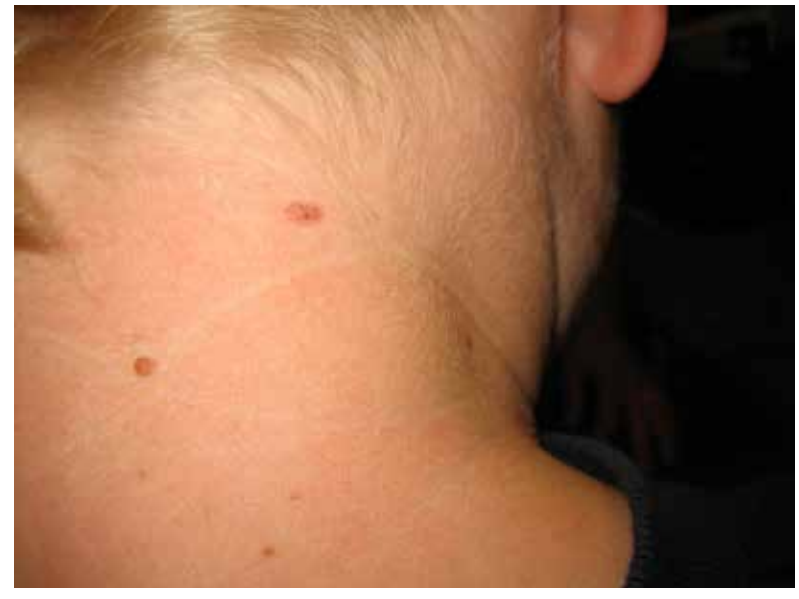


Melanocytic Nevi

Melanocytic nevi, commonly called moles, are a very common skin lesion made of collections of melanocytes. By the age of ten, the average Caucasian child will have approximately 15-30 nevi while African, Asian and Native American children will have approximately 5-10 nevi.[5]

Acquired melanocytic nevi (AMN) tend to appear in early childhood (Figure 3). AMN are classified by the location of melanocytes in the skin; junctional nevi have melanocytes located in the dermal-epidermal, compound nevi have melanocytes in the dermo-epidermal junction as well as in the deeper dermis, and intradermal nevi have melanocyes within the dermis. In childhood AMN are typically brown to black macules (junctional nevi), brown papules (compound nevi) in adolescence and adults, and

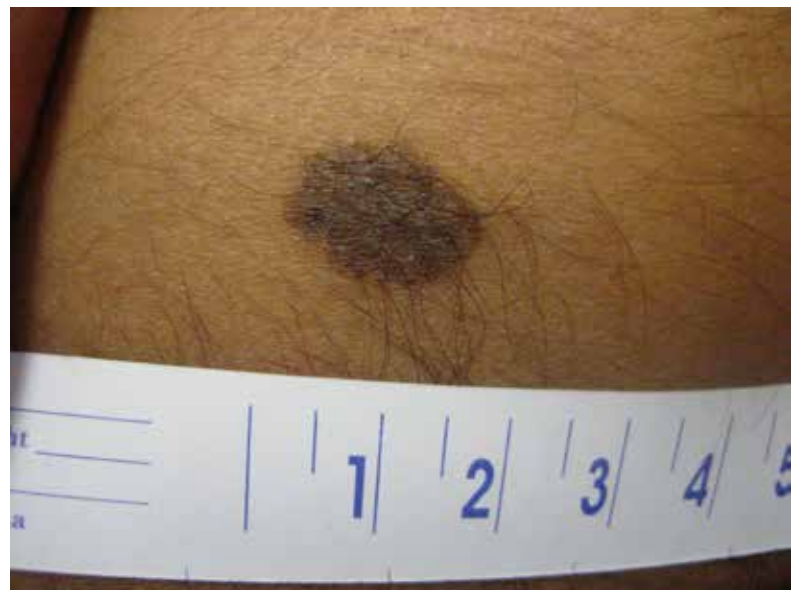
Figure 3: Acquired Melanoctic Nevus



flesh colored papules (intradermal nevi) in older adults. They grow in size and number until the third or fourth decade of life and then slowly regress. The lifetime risk of a AMN transforming into malignant melanoma (MM) is 1/10000, and >50% of (MM) occur de novo.[5] Increased risk factors for MM include family history of MM, excessive sun exposure, and light colored skin.[5] The appearance of MM in children is different than in adults. Pediatric MM are often not pigmented, have a uniform color, are nodular or thickened, have a variable diameter, and tend to occur de novo.[5] In children with multiple AMN most of their nevi will have a similar appearance; a good rule of thumb is to look for the "ugly duckling" mole. Children with AMN should monitor their moles regularly and report any concerning changes to a health care provider. AMN can be removed for cosmesis.

In contrast to AMN, congenital melanocytic nevi (CMN) are present at birth but are not always apparent in the first few months of life. CMN are classified by the projected adult size and are divided into small (<1.5cm), medium (M1: 1.5-10cm, M2: >10-20cm), large (L1: >20-30cm, L2>30-40cm), and giant (G1: >40-60cm, G2: >60cm) subtypes.[6] CMN present as tan to black papules or plaques, and often have well defined borders (Figure 4). While most are initially smooth, many develop hypertrichosis, nodularity, and a rough or verrucous surface.[5]

Figure 4: Congenital Melanocytic Nevi (CMN)



The risk of malignant melanoma (MM) is greatest in large and giant CMN, with a lifetime risk of 2-5%. ~50% of patients with MM in the setting of a large or giant CMN will present with the malignancy within the first five years of life.[5] Small and medium CMN have less than a 1% lifetime risk of MM and if malignant transformation occurs, it tends to occur after puberty.[5] All CMN should be regularly monitored. Large and giant CMN should be monitored regularly by a healthcare provider with experience in CMN for any concerning changes, even after surgical excision.[5] Small and medium CMN can be monitored by parents with pictures at baseline and at regular intervals along with education of concerning changes to watch for.[5] CMN can be associated with neurocutaneous melanosis, characterized by abnormal aggregations of nevomelano-

cytes within the central nervous system, with the greatest risk in patients with >20 pigmented satellite lesions.[5]

CMN can be removed by surgical excision; with the decision and timing of removal determined by the size, location and appearance of the lesion, cosmesis and patient preference. Children with CMN should take appropriate sun precautions.

Post-inflammatory hyperpigmentation

Post inflammatory hyperpigmentation (PIH) is the term for hyperpigmentation that occurs after an insult to the skin (Figure 5) and is one of the most common causes of hyperpigmentation.[2] Insult to the skin can result from exogenous (physical trauma, irritants, and friction) or endogenous (inflammation from acne vulgaris, eczema and other dermatoses) factors.[2] The risk of PIH is higher in children with darker skin types and persists longer.[1] Most episodes of PIH last for several months following the insult and resolve on their own with no treatment required. If there is ongoing inflammation a topical anti-inflammatory may be used.[2]

Ephelides

Ephelides, commonly called freckles, are small, light brown macules (Figure 6) that appear in areas exposed to the sun.[6] Ephelides can be seen in early childhood and tend to be more pronounced in the spring and summer and fade during winter. Ephelides fade and tend to become smaller and fewer in number when out of sun exposure.[2] They do not require treatment. For cosmesis, makeup can be worn and the development of ephelides can be curtailed with sun avoidance and applying sun protection.[2]

Acanthosis nigricans

Acanthosis nigricans (AN) is a dark brown, velvety plaque that occurs

Figure 5: Post Inflammatory Hyperpigmentation

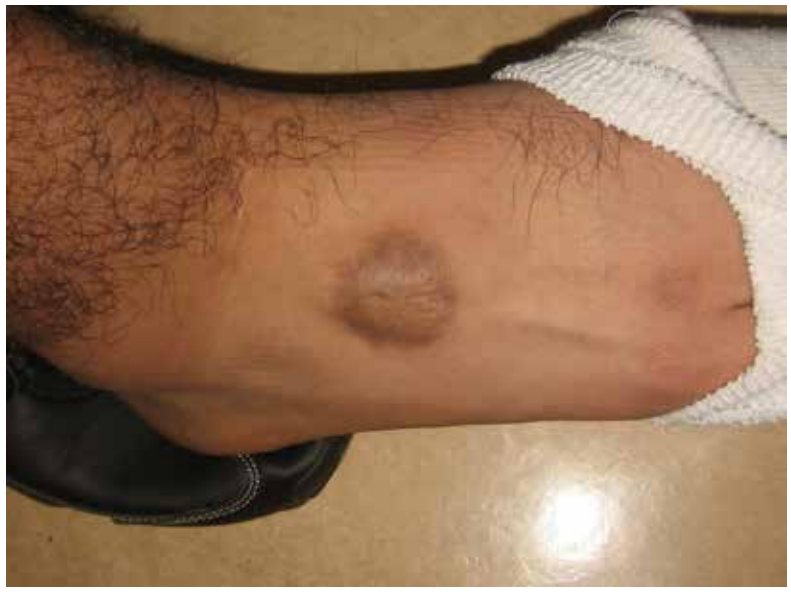
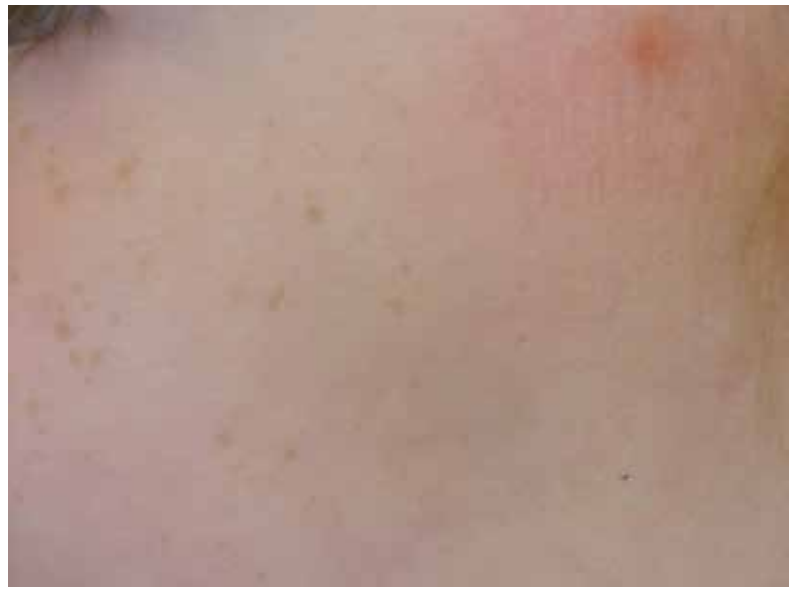


Figure 6: Ephelides



in intertriginous areas such as the axillae and neck folds (Figure 7).[2] The dark color of AN is caused by hyperkeratinization of the skin, not from an increase in pigment. AN is typically a cutaneous marker of insulin resistance, and is associated with diabetes mellitus, polycystic ovarian syndrome and obesity. It can also be associated with malignancies, although this is usually in adults, medications and several syndromes.[2] Patients with AN should be investigated for hyperinsulinemia.[2] The plaques do not require treatment unless there is cosmetic concern. Topical therapies may work in some patients, and some modalities for therapy include retinoids, keratolytics or lactic-acid.[2]

Phytophotodermatitis

Phytophotodermatitis is a phototoxic reaction caused by a chemical compound (furocoumarin, or psoralens) found in a number of common plants including: lemons, limes, parsnips, carrots, dill, parsley, celery, figs, and giant hogweed.[2] Phototoxic reactions are a non-immune response to UVA light following cutaneous exposure or ingestion of a photosensitizing substance. Lesions appear in sun exposed areas within a day of exposure as erythema, bullae and edema in a pattern that follows the cutaneous exposure (Figure 8). As the acute lesions resolve they are replaced by hyperpigmentation and desquamation. The hyperpigmentation fades over a period of weeks to months and typically requires no treatment.[2] Severe burns may require debridement and wound closure.

Fixed Drug Eruption

Lesions associated with fixed drug eruptions occur 1-2 weeks after initial drug ingestion, and as soon as 30 minutes after subsequent exposure.[2] Lesions present as well circumscribed, round or oval, erythematous and edematous

Figure 7: Acanthosis Nigricans

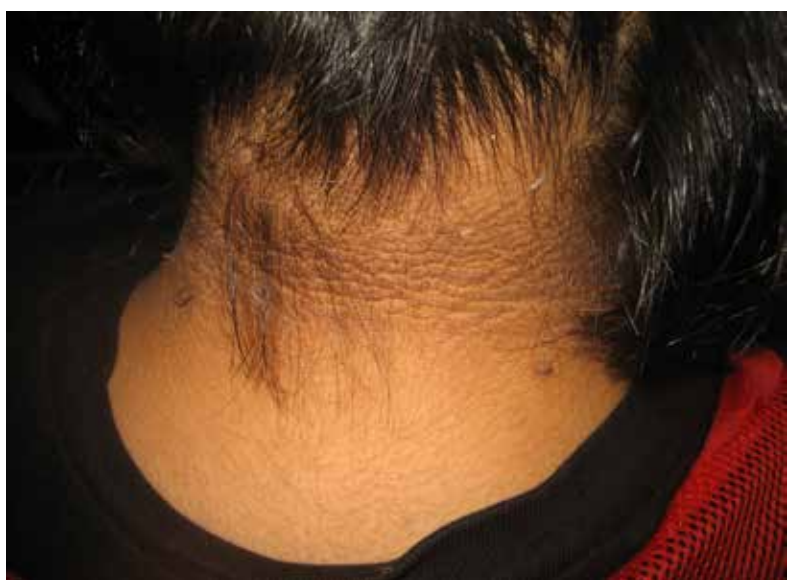
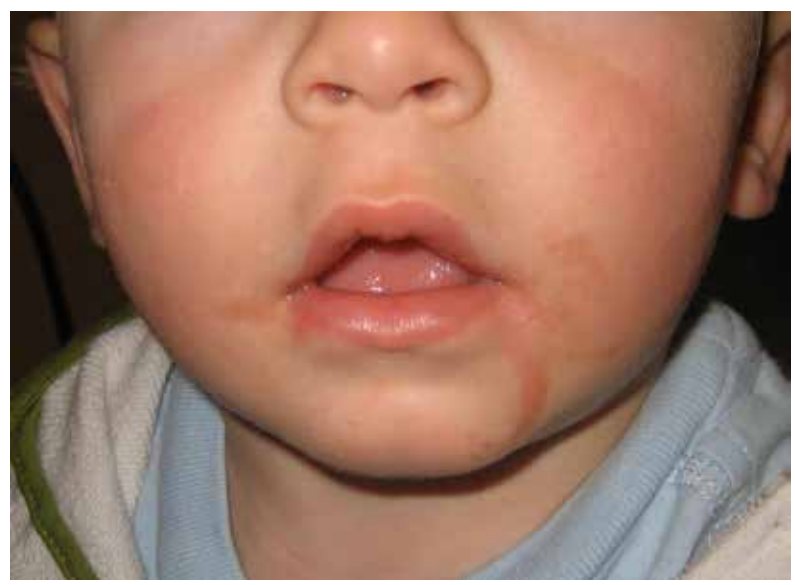


Figure 8: Phytophotodermatitis



plaques or bulla and are pruritic (Figure 9).[2] They tend to appear on the lips, hands, trunk and genitals.[2] After the lesions resolve, the affected areas have intense residual hyperpigmented. The most common cause is sulfa drugs, but other etiologies include over-the-counter medications such as acetaminophen and ibuprofen.[2] Once a causative medication has been identified, it should be avoided. There is no treatment required for the lesions. Antihistamines can be given to help with the pruritus.

Terra firma-forme dermatosis

Terra firma-forme dermatosis (TFFD) is an idiopathic condition that presents as 'dirt colored' (tan to dark brown) hyperpigmented, papillomatous plaques with a stuck on appearance (Figure 10). They are most common on the neck, trunk and umbilicus.[7] TTFD is caused by retention hyperkeratosis but the mechanism responsible for this is not known.[7] These lesions

Figure 9: Fixed Drug Eruption

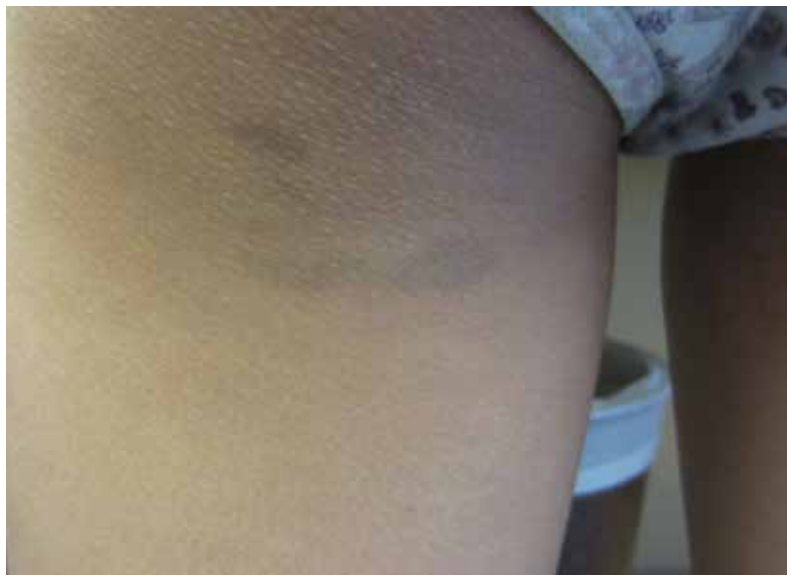
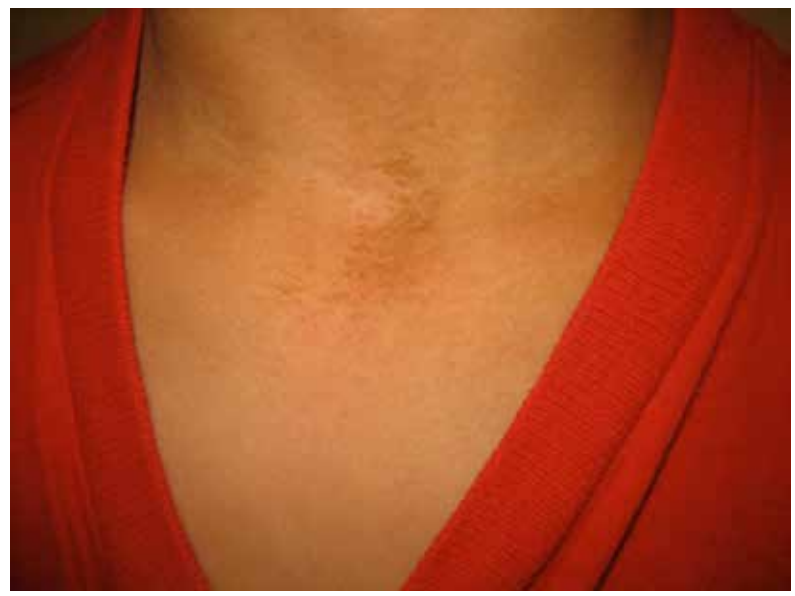


Figure 10: Terra firma-forme dermatosis



cannot be removed with soap and water but are easily removed by 70% alcohol.[8] TFFD is a clinical diagnosis made based on the morphology and the disappearance of lesions after 70% alcohol is applied.

UNCOMMON CONDITIONS

Incontinentia Pigmenti

Incontinentia Pigmenti (IP), or Bloch-Sulzberger Syndrome, is a rare, X-linked dominant disorder.[2] It is a multisystem disease affecting the skin, central nervous system (CNS), teeth and eyes. IP typically presents in four stages. Neonates have inflammatory vesicular or bullous lesions that follow the Blaschko lines and heal spontaneously.[2,9] In children aged 2-6 months of age, the lesions become hyperkeratotic and verrucous.[7] In the first few years of life the lesions evolve into hyperpigmented patches (Figure 11).[9] By early adulthood the final stage occurs with hypopigmentation

Figure 11: Incontinentia Pigmenti

and atrophy.[9] The skin lesions of IP tend to clear spontaneously and do not require treatment.[2] Children with IP require regular screening and management for the associated CNS, teeth and eye complications.

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disease associated with cutaneous photosensitivity due to decreased DNA repair following damage by UV radiation.[2] Patients with XP develop small brown to black macules following UV exposure that resemble freckles but do not fade.[1] With repeated UV exposure the skin may atrophy, develop telangiectasias and is at a higher risk of skin cancers.[1] XP should be suspected in infants that develop significant sunburns or excessive photodistributed lentigines and ephelides. The diagnosis can be made by genetic testing.[1] Management of XP involves screening for cutaneous malignacies and protective measures including: avoiding UV exposure, sunscreen, protective clothing, sunglasses and protective window coatings.[1] Patients will require vitamin D supplementation.[1]

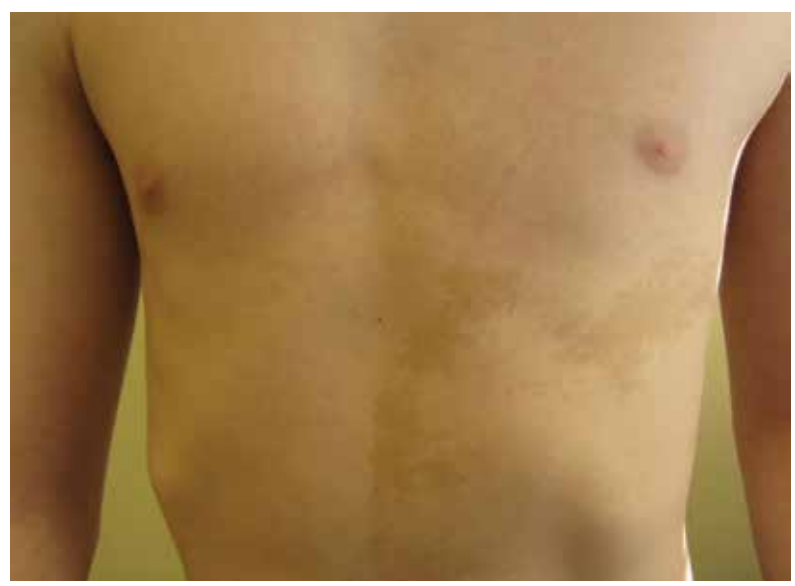
Segmental pigmentation disorder

Segmental pigmentation disorder (SPD), also known as mosaic hyperpigmentation or pigmentary mosaicism, is a result of cutaneous somatic mutations.[1] It usually occurs sporadically and there is no associated family history.[10] The lesions are typically hyperpigmented patches (Figure 12) (but can be hypopigmented), most commonly on the trunk, in a 'checkerboard' pattern of alternating areas of hyperpigmentation with a sharp midline demarcation.[8] No treatment is required for these skin lesions.

Congenital Smooth Muscle Hamartoma

Congenital smooth muscle hamartomas (CSMH) are benign lesions

Figure 12: Segmental Pigmentation Disorder



caused by excess smooth muscle tissue in the dermis layer of the skin that are typically present at birth. They appear as a skin colored to tan plaque with hypertrichosis (Figure 13).[1] They are most commonly seen on the trunk, especially the lumbosacral area. There is no malignant potential of CSMHs and treatment is unnecessary unless for cosmesis.[1]

Plexiform Neurofibroma

Plexiform neurofibromas (PN) are considered pathognomonic for neurofibromatosis Type 1 (NF1). They occur along the length of a nerve and have a variable appearance, from barely palpable plaques to lesions that feel like a 'bag of worms' (Figure 14).[2] Often they occur within a CALM and can have associated hypertrichosis.[2] With time, there is hypertrophy of underlying tissue and bone, which can affect sensation, cause pain and weakness, or muscle atrophy.[2] Over time PNs will grow which can cause significant disfigurement and interfere with function.[1] Surgical removal of PN is an option but it may be difficult to remove the entire tumor in many cases. Treatment with MEK (mitogen-activated protein kinase) inhibitors and imatinib (a tyrosine kinase inhibitor) have been shown to decrease the size of PNs.[2] Sirolimus (an mTOR inhibitor) can be used for pain but does not appear to decrease the size of the tumor.[2]

Figure 13: Congenital Smooth Muscle Hamartoma

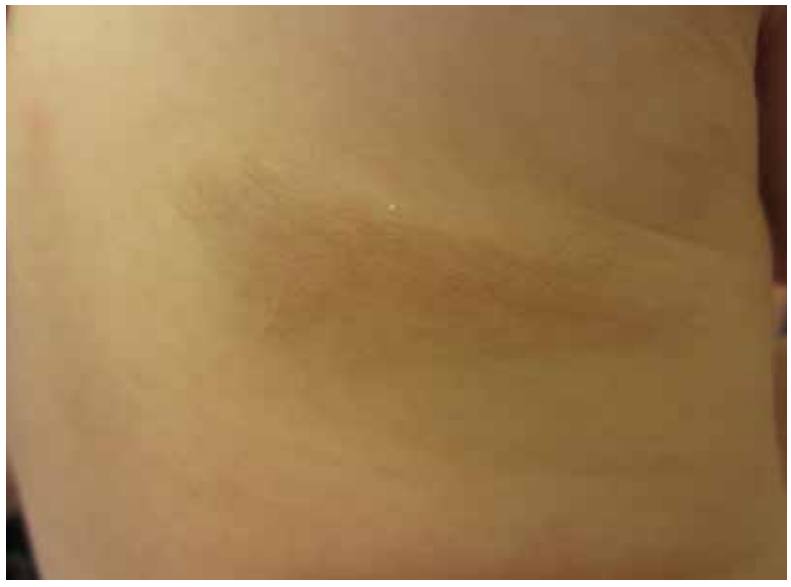


Figure 14: Plexiform Neurofibroma

Summary

Hyperpigmented lesions are an extremely common finding in the pediatric population. There are numerous conditions that can present with hyperpigmentation. Differentiation between these conditions is largely based on the morphology of the lesion and whether it is congenital or acquired. Most hyperpigmented lesions in children do not require treatment unless for cosmesis. Many of the

SUMMARY OF KEY POINTS

1. Most hyperpigmented lesions in children do not require treatment aside from for cosmesis.
2. Features of malignant melanoma in children include: non-pigmented, uniform color, variable diameter, nodular lesions, and occurring de novo.
3. Parents and children should be warned that melanocytic nevi will grow as their child grows, but growth should be proportionate.
4. The risk of melanocytic nevi becoming malignant melanoma in children is very small.

acquired conditions including post inflammatory hyperpigmentation, ephelides, phytophotodermatitis, and fixed drug eruption will fade or resolve over time. Benign lesions that do not require monitoring include isolated café au lait macules, epidermal nevi, terra-firma forme dermatosis and congenital smooth muscle harmartomas. Children with congenital and acquired melanocytic nevi should be monitored by a healthcare professional for any concerning changes. Children with multiple café au lait macules, incontinentia pigmenti, plexiform neurofibroma and acanthosis nigricans should be evaluated for associated diseases.

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CLINICAL PEARLS

In children with numerous melanocytic nevi, a good rule of thumb is to look for the 'ugly duckling' mole.

To track lesions over time, parents can develop a routine of taking a picture each year on the child's birthday.

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