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Pediatric Skin of Color

Springer

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This book is dedicated to my family: Wan Ching, Ern Wei, and Ern Ying for their continuous love, support, patience, and understanding in allowing me time to write and edit, and make everything worthwhile.

Yong-Kwang Tay, FRCP

This book is dedicated to the most important people in my life: my mentors, Prof. Ramón Ruiz-Maldonado and Prof. Lourdes Tamayo, and my daughters, Sofía and Natalia Deveaux-Durán. From all of them I have learned the pleasure of teaching and sharing my experience and knowledge.

Carola Durán-McKinster, MD

This book is dedicated to my family and dearest colleagues who have made this possible: my mentors who shared their skills with me and showed me a path of educational exploration and on-going learning. But most importantly, this book is dedicated to my parents and Harry for their unconditional love, advice and support during the process and throughout my career.

Nanette B. Silverberg, MD

Preface

In the past, the majority of patients seen in the United States and Europe were fair-skinned individuals; up to the 1970s and the early 1980s, most of the published studies in dermatology were done in this population. With globalization of the economy and the advance of convenient international travel, the proportion of people of color (POC) in North America and Europe are rapidly increasing. Based on the latest (2010) US Census data, it has been estimated that by July, 2013, 63% of the US population would be non-Hispanic whites, while the rest would be POC, including Hispanic whites (1). The need for an increased understanding of skin conditions in POC is reflected by the formation of the Skin of Color Society by Susan Taylor, MD, in 2004, the establishment of centers in several academic institutions focusing on POC, and the publication of several general dermatology textbooks and atlases on this topic. This demographic shift is most notably seen in the number of skin of color-related sessions at the annual meetings of the American Academy of Dermatology: in 1995, there were 3 sessions; in 2005, 5 sessions; and in 2015, 21 sessions.

Pediatric dermatology is an established subspecialty in dermatology. The 13th World Congress of Pediatric Dermatology, currently being held every 4 years, is scheduled for 2017. There are pediatric dermatology societies worldwide. In the United States, there are 31 pediatric dermatology fellowship programs approved by the American Board of Dermatology (ABD), leading to subspecialty certification of the graduates by the ABD.

Drs. Tay, Durán-McKinster and Silverberg are to be congratulated for editing this first textbook on skin of color in the pediatric patient population; they are eminently qualified to do so. Dr. Tay practices in Changi General Hospital in Singapore, a city-state that is known for its multicultural and multi-ethnic population. Dr. Durán-McKinster practices in Mexico City, a city whose inhabitants have a wide range of skin phototypes. Dr. Silverberg practices in New York City, and is affiliated with the first Skin of Color Center in the United States. They have organized an international group of authors to cover all aspects of pediatric dermatology.

This textbook would certainly appeal to a worldwide readership of dermatologists, pediatric dermatologists and pediatricians. It will be a frequently used reference in the daily practice of all of us.

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Part I

Biology of Normal Skin, Hair and Nails

Development and Biology of East Asian Skin, Hair, and Nails

1

Mark Jean-Aan Koh

Abstract

People of skin of color comprise the majority of the world's population and Asian people comprise more than half of the total population of the world. East Asia encompasses a subregion of Asia that may be defined in geographical or cultural terms. Geographically, it covers about 28 % of Asia and is populated by more than 1.5 billion people, just over one-fifth of the world's population. Countries traditionally classified as being part of East Asia include China, Japan, North and South Korea, Mongolia, and Taiwan. Historically, many societies in East Asia have been part of the Chinese cultural sphere. However, with the increasing mobility of the world's population over the past two centuries, people of East Asian descent have fanned out to not only other parts of Asia but also to all other continents.

Keywords

Biology • East Asian Skin • Hair • Nails • Pigmentation • Melanosomes • Melanocytes

Development and Biology of Pigmentation in East Asian Skin

- Melanocytes migrate as neural crest cells to the epidermis where they reside within the basal epidermis and hair bulb matrix.
- Difference in skin color is due to variations in number, size, and aggregation of the melanosomes.
- Pigmentary skin disorders, e.g. post-inflammatory dyspigmentation, melasma, and lentigines, are commonly seen in East Asians.

The hallmark biological feature of people of skin of color is the amount and distribution of melanin in the skin. Melanin is synthesised by melanocytes within melanosomes [1, 2]. Melanocytes migrate as neural crest cells to the epidermis from the 18th week of gestation [3]. In the skin, the melanocytes are resident within the basal epidermis and hair bulb matrix. Each melanocyte in the basal layer produces dendrites that are associated with approximately 36 epidermal keratinocytes [4]. Tyrosinase, an enzyme critical to the formation of melanin, is formed within the Golgi bodies of melanocytes and transferred to melanosomes. Tyrosinase converts tyrosine to dopa, which is then converted to dopaquinone. Dopaquinone is further oxidised to form eumelanin, which is brown-black in color. In contrast, pheomelanin appears yellow-red and is formed by a shunt in the eumelanin pathway. Melanosomes are ultimately transferred to keratinocytes either as aggregated, complex particles or discrete, single particles [5].

The difference in skin color between different races is due to variations in number, size, and aggregation of the melanosomes found in melanocytes and keratinocytes [6]. The absolute number of melanocytes does not vary between races. The melanosomes of East Asian subjects have been found to be in aggregates but have a more compact configuration compared to Caucasian skin, in which melanosomes are more grouped. In contrast, the melanosomes in Black skin are individually dispersed and not aggregated (see Tang N, et al. Chapter 2; Developmental Biology of Black Skin, Hair, and Nails) [7].

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Sun exposure can also affect the grouping of melanosomes. Asian skin exposed to sunlight has been found to have more non-aggregated melanosomes compared to non-exposed skin, which have more aggregated melanosomes [8]. In addition, the epidermal distribution of melanosomes has been shown to vary between races, with melanosomes distributed throughout the entire epidermis in black skin compared to white skin, where melanosomes are seen only in the basal and spinous layers [9]. A study in Thai subjects showed melanosomes distributed throughout the entire epidermis with dense clusters in the basal layer and heavy pigmentation in the stratum corneum [10].

Melanin and melanosomes have been found to impact on photoprotection [11]. Melanin offers protection from UV light by absorbing and deflecting UV rays [12]. In addition, the more individually dispersed the melanosomes, the better the photoprotection [12]. Minimal erythema dose (MED) has also been shown to be affected by melanin and melanosomes. Subjects with darkly pigmented skin have an average MED 15–33 times more than subjects with white skin [8]. A study on 101 Japanese women, comparing skin color and MED, showed that the greater the epidermal melanin content, the less severe the reaction to sunlight [13]. Despite this, however, significant photodamage can still occur in pigmented Asian skin in response to chronic ultraviolet light exposure, e.g. keratinocyte atypia, epidermal atrophy, dermal collagen and elastin damage, and hyperpigmentation [10]. This may be partly attributed to the fact that melanin may not be an efficient absorber of UVA wavelengths. The incidence of skin cancers, e.g. basal cell carcinoma, squamous cell carcinoma, and melanoma, in East Asian individuals is relatively low compared to whites, but does occur.

The melanin content and dispersion pattern of melanosomes has been thought to be largely responsible for providing protection from the carcinogenic effects of UV radiation [14, 15]. Apart from incidence, differences in site distribution, stage at diagnosis, and histologic subtype occur in melanoma occurring in East Asians compared to whites. In particular, acral lentiginous melanoma is the most common form of melanoma occurring in Asians. Despite the low incidence, the prognosis of melanoma in Asians is not as good as in Caucasian populations, likely due to more advanced stages at diagnosis. This is due to a combination of factors like decreased individual skin surveillance and decreased suspicion of the disease in examining physicians. Differentiation of melanonychia, which is very common in adult Asians (e.g. Japanese), from acral lentiginous melanoma requires careful review of lesion width, coloration, dermoscopy, the presence of Hutchinson's sign, and evolution of the lesion.

Due to the biology of melanin and melanosomes in Asian skin, pigmentary disorders are much more common compared to white subjects. Post-inflammatory hyperpigmentation, melasma, and solar lentigines are extremely common pigmentation problems presenting in East Asian adults. Ultraviolet light-induced changes typical of young Caucasian children, e.g. spider angiomas and ephelides, are uncommon in East Asian children. These problems should not be treated as trivial cosmetic issues, as they can lead to significant psychosocial impairment in affected individuals.

Development and Biology of the Epidermis in East Asian Skin

- In normal individuals, keratinocytes take approximately 4 weeks to be shed from the epidermis.
- After birth, the skin barrier takes a few weeks to achieve maturity.
- Skin lipids and filaggrin in the stratum corneum contribute to the integrity of the skin barrier.

The thickness of the human epidermis averages 50 μm and is made up of four or five layers, with the most superficial layer being the stratum corneum, followed by the stratum granulosum, stratum spinosum, and stratum basale. On the palms and soles, a layer known as the stratum lucidum is found between the stratum corneum and stratum granulosum. The keratinocytes that make up the bulk of the epidermis originate from the stem cell pool in the basal layer of the epidermis. The keratinocytes then undergo maturation as they move upwards towards the stratum corneum. On average, keratinocytes require 2 weeks to migrate from the stratum basale to the stratum granulosum, whereupon they lose their nuclei and differentiate into the corneocytes of the stratum corneum. In normal individuals, it takes approximately another 2 weeks for the corneocytes to shed from the skin. This duration can be shortened or lengthened in diseased states of the skin, e.g. psoriasis.

The epidermis is derived from the ectoderm in the human embryo. During the first month of gestation, the epidermis exists as a single layer, known as the periderm. Stratification of the epidermis begins about the eighth week of gestation and is mostly complete by the second trimester. Epidermal keratinisation begins during the second trimester and achieves maturation by the middle of the third trimester. The superficial keratinocytes undergo maturation as keratinisation progresses, with increase in the number of keratohyalin granules and lamellar bodies. By the mid-third trimester, the epidermal layers are morphologically similar to adult skin. However, skin barrier function only really achieves maturity a few weeks after birth [16, 17].

The data on racial differences in the structure and function of the stratum corneum have been conflicting, with even less studies performed on East Asian subjects. Some studies have shown the stratum corneum to be more compact in black compared to white subjects, with possibly more cornified layers and better epidermal barrier function [18, 19].

Corcuff et al., in a study comparing African Americans, white Americans, and Asians of Chinese descent showed increased spontaneous corneocyte desquamation in blacks compared to the Chinese and white group, which were almost similar [20]. Studies on the thickness of the stratum corneum between races have shown conflicting results, with most of these studies comparing the epidermis in black and white subjects [9, 21]. There are a handful of studies documenting differences between East Asian skin epidermis and other racial skin types. In a very recent study, the epidermis of African skin was found to be thicker with deeper rete ridge projections than East Asian skin [22].

The barrier properties of the skin can be predicted by the structural integrity of the stratum corneum [23]. The stratum corneum, being metabolically inactive, is penetrated by passive diffusion of substances. Penetration through cutaneous appendages, e.g. hair follicle wall, plays a smaller role [24, 25]. Studies on racial differences in the percutaneous absorption of various chemicals have produced conflicting results [26–30]. The susceptibility of the skin to irritants is also thought to be determined by the differences in the biological structure of the stratum corneum. However, the data from studies done to compare inter-racial skin susceptibility to irritants have also been somewhat controversial, with most studies done comparing white and black subjects [31–34]. A study by Goh and Chia evaluated skin irritation to 2 % sodium lauryl sulphate (SLS) by measuring skin water vapour loss (SVL) in 15 fair-skinned Chinese, 12 Malays with darker skin, and 11 Indians with very dark skin. No significant difference was found in mean baseline SVL values and SVL values after exposure to SLS between the three different groups [35]. Kompaore et al. compared the barrier function of the stratum corneum between African blacks, white Europeans, and Asians. Baseline trans-epidermal water loss (TEWL) measurements were found to be significantly higher in Asian and black subjects compared to white subjects. The authors concluded that black and Asian skin may have a more compromised barrier function compared to skin of white Europeans, leading to greater susceptibility to irritants [36]. However, Reed et al. found no significant differences in baseline TEWL among subjects with skin types II and III (Asian and whites) versus subjects with skin types V and VI (African American, Filipino, Hispanics). However, subjects with skin types V and VI demonstrated superior barrier integrity and recovery after exposure to skin irritants [19]. Muizzuddin et al. found that, compared to African-American and Caucasian skin, East Asian skin had the weakest barrier properties and lowest degree of maturation [37]. Both filaggrin and skin lipids in the stratum corneum are known to contribute to the integrity of the skin barrier. In addition, an optimal lipid composition is important to aid in this barrier function [38]. Jungersted et al. have found significant differences in the ceramide/cholesterol ratios between different racial groups with Asians having the highest ratio compared to white-skinned individuals and Africans [39].

Development and Biology of the Dermis in East Asian Skin

The cells of the dermis can be seen under the presumptive epidermis by 6–8 weeks gestation. Unlike the epidermis which is derived solely from ectoderm in the human embryo, the origin of the dermis is variable depending on the body site. Early fibroblasts found in the dermis are thought to be pluripotent cells that can differentiate into other cell types, e.g. fibroblasts and adipocytes. Early dermal cells are known to already be able to produce most types of collagen and the microfibrillar components of elastic fibres. However, these proteins are initially not fully assembled into large fibres. In reverse to the ratio seen in adult dermis, the ratio of collagen III to collagen I in embryonal skin is 3:1. By the early second trimester, the papillary dermis with its finer collagen weave becomes distinct from the lower reticular dermis with its larger, thicker collagen fibres. Elastic fibres become apparent around 22–24 weeks gestation. At birth, the neonatal dermis is thinner and more cellular than adult dermis. Subcutaneous fatty tissue begins to accumulate during the second trimester and throughout the third trimester, when the distinct lobules separated by septae become visible. Although the blood vessels in the dermis may be seen by the end of the first trimester, there is subsequent extensive remodelling that occurs not only throughout gestation, but also after birth [40]. Nerves in the dermis are formed by the end of the first trimester and generally follow the distribution of the blood vessels [16, 17].

Although there has been no proven difference in thickness of the dermis between races, there have been differences shown at cellular level. Langton et al. showed that East Asian skin dermis was found to have less collagen I and collagen III than African skin but more than Eurasian (people of mixed Asian and European descent) skin. While fibrillar collagen confers tensile strength, the elastic fibre system in the dermis confers resilience and passive recoil. Fibrillin-rich microfibrils and the microfibril-associated protein fibulin-5 (found in oxytalan and elaunin elastic fibres of papillary dermis) were found to be reduced in both Eurasians and East Asians compared to Africans. However, glycosaminoglycan content was found not to be statistically different between the three races [22].

Development and Biology of the Dermal–Epidermal Junction in East Asian Skin

The dermal–epidermal junction (DEJ) is an important structure in the skin. It develops from a simple basement membrane in the embryo into a complex, multilayered structure during the

second trimester. The embryonal DEJ contains molecules common to all basement membrane systems (e.g. type IV collagen, laminin, heparin sulphate, and proteoglycans). At the same time as stratification of the epidermis occurs during the mid-first trimester, the DEJ acquires specific skin-associated components, including hemidesmosomes, anchoring filaments, anchoring fibrils, type VII collagen, laminin 332, and BP180. During development, the rete ridge pattern and dermal papillae become more obvious. Langton et al. found that collagen VII was more widely distributed in East Asian skin compared to the more discrete distribution seen in African skin. In contrast, there was no significant difference in the distribution of laminin-332 and integrin β4 between East Asian, Eurasian, and African skin [22].

Development and Biology of Hair Follicle Units in East Asian Skin

- Asian hair is round or circular and has the largest cross-sectional area compared to Caucasians and Blacks.
- The hair cycle consists of anagen, catagen, and telogen, with hairs being shed soon after telogen.
- The size of melanin granules in Chinese hair is smaller compared to Blacks.

Hair follicle development first occurs on the scalp and face, and progresses caudally and ventrally in the fetus. The formation of the hair follicle is initiated by signals from the dermis, directing the basal cells of the epidermis to focally aggregate, forming the follicular placode. The placode sends signals to instruct the underlying dermal cells to condense to form the presumptive dermal papilla. The dermal papilla then directs the cells of the placode to proliferate and extend deeper into the dermis. Two distinct bulges develop in the superficial part of the developing hair follicle. The more superficial bulge develops into the associated sebaceous gland, and the deeper bulge indicates the point of insertion of the future arrector pili muscle which also contains the presumptive follicular stem cells. The seven concentric layers of the hair follicle become apparent during the second trimester. From innermost to outermost layers they consist of the medulla, cortex, hair shaft cuticle, inner root sheath cuticle, the Huxley and Henley layers of the inner root sheath, and the outer root sheath. The lower portion of the hair follicle keratinises without forming a granular layer (trichilemmal keratinisation), while the upper portion of the hair follicle is continuous with the interfollicular epidermis and undergoes keratinisation similar to that of the epidermis, with a granular layer present. The hair canal is fully formed by the mid-second trimester. The hair cycle has three phases: anagen, the active growing phase, catagen, a short degenerative phase, and finally, telogen, the resting phase. The hairs are shed soon after the telogen phase and the entire cycle begins again. This hair cycle continues throughout the lifetime of the individual [16, 17].

The density of hair follicle orifices on the scalp and calves of Asian subjects has been shown to be less than the density in Caucasian skin but similar to the density in African skin [41–43]. The hair of Asian subjects is the most nearly round or circular and has the largest cross-sectional area compared to Caucasian subjects. Black subjects have the longest major axis, giving the hair a flattened elliptical shape [44]. The volume of the follicular infundibulum has been found to be different among different ethnic groups, with Asian hair follicles having the smallest volume compared to Caucasians and Africans [45]. This has been postulated to have significance in the percutaneous absorption of substances through the skin as the follicular infundibulum may serve as a reservoir for these topically applied substances [46]. The size of melanin granules in Asian Chinese hair has been found to be smaller than the hair of black subjects [47]. Khumalo et al. reported that African hair had a tendency to form knots and longitudinal fissures and splits along the hair shaft compared to hair of Asian and white subjects. The majority of the tips of African hair had fracture ends indicating breakage, whereas the majority of white and Asian hair was shed [48].

Sebaceous glands are attached to the hair follicle by the pilosebaceous duct and are found on all skin surfaces except the palms and soles. Sebaceous gland development follows that of the hair follicle, with the presumptive sebaceous gland appearing at around 13–16 weeks gestation as bulges from the hair follicle. The outer proliferative layer generates lipogenic cells that accumulate lipids (sebum) until they become terminally differentiated and disintegrate to release sebum into the hair canal. Sebum contains a mixture of squalene, cholesterol, cholesterol esters, wax esters, and triglycerides. Triglycerides are hydrolysed to free fatty acids by bacterial lipases. In a study by Hillebrand et al., African Americans were shown to secrete significantly more sebum than East Asians [49]. However, another study by Abedeen et al. showed that there was no statistical significance in sebum secretion rate among whites, blacks, and Asians [50]. There are few studies on the differences in sebum composition and race. Yamamoto et al. found that Japanese subjects had a greater predominance of straight chain fatty acids in their sebum than branched chain fatty acids compared to Caucasian subjects [51].

Development and Biology of Sweat Glands in East Asian Skin

- There are three types of sweat glands: eccrine glands, apocrine glands, and apoeccrine glands.
- Apocrine glands, functional during the third trimester, become quiescent after birth and regain activity again during puberty.

- The effect of race on the size and function of sweat glands is less than the effect of climate, with a greater density of actively sweating glands in tropical climates.

There are three types of sweat glands that can be found on the skin. Eccrine sweat glands can be found almost over the entire body, with variable densities from region to region. They play a key role in the thermoregulatory system of the body. Apocrine sweat glands are larger and mostly limited to the intertriginous regions, e.g. axilla and groin. They develop from the pilosebaceous unit and become active just before puberty. Their physiological role remains uncertain. A third type of sweat gland, the lesser-known apoeccrine gland, develops at puberty from the eccrine glands in the axilla. This type of gland shows a segmental or diffuse apocrine-like dilatation of its secretory tubule but has a long, thin duct that does not open into a hair follicle [52].

Eccrine gland development begins on the palms and soles from about 6–8 weeks gestation. It starts with the formation of mesenchymal bulges or pads on the palms and soles. Associated ectodermal ridges appear in the epidermis overlying these mesenchymal pads at about 10–12 weeks gestation. At 14–16 weeks gestation, eccrine gland primordia start to bud along the ectodermal ridges and elongate as cords of cells entering the mesenchymal pads. Glandular structures form at the terminal end of the buds with appearance of secretary and myoepithelial cells. Canalisation of the dermal portion of the ducts is complete by 16 weeks gestation, while canalisation of the epidermal portion of the duct occurs only by 22 weeks gestation. Eccrine glands from other parts of the body apart from the palms and soles start to form only from the fifth month of gestation. Apocrine glands typically arise from the upper portion of the hair follicle and begin development only about the fifth month of gestation. The cords of cells elongate over a few weeks and the clear cells and dark cells can be visualised by 7 months gestation. The apocrine glands are transiently functional during the third trimester but become quiescent shortly after birth, only to become active again during puberty.

The effect of race on the size and function of sweat glands is known to be less than the effect of climate. There is probably a greater density of actively sweating glands in tropical climates rather than actual real differences in the number of sweat glands. A study by Kawahata and Saramoto of the Ainu, a Japanese ethnic group, supports the influence of climate on sweat glands. They demonstrated that Ainu born in Japan who migrated to the tropics had the same number of sweat glands as Ainu born in Japan who continued to live in Japan. However, Ainu born in the tropics had a larger number of sweat glands than the other groups [53]. Early studies had documented that black subjects have larger and greater numbers of apocrine glands compared to Chinese and Caucasian subjects. Black subjects may also secrete more apocrine sweat and were more turbid [54].

Development and Biology of Nails in East Asian Skin

- Development of the nail unit is associated with development of the limb bud.
- The distal nail matrix in people of color contains more active melanocytes than Caucasians.

Nail development begins at about 8–10 weeks gestation and is completed by the fifth month of gestation. The nail bed first appears as visible folds at 8–10 weeks. An ectodermal wedge invaginates into mesenchyme along the proximal end of the nail field, forming the proximal nail fold. The nail matrix cells which form the nail plate are seen ventral to the proximal nail fold. Keratinisation of the nail bed begins around 11 weeks gestation. The initial nail is shed and replaced by a harder nail plate that emerges from under the proximal nail fold during the fourth month gestation. The development of the nail unit is integrally associated with limb bud development, involving signalling molecules and transcription and growth factors, including Wnt-7a, en-1, and LMX1-b [55].

The nail unit consists of the proximal nail fold, the matrix, the nail bed, and the hyponychium. The nail plate, a flat, rectangular, hard structure sits on top of the digits and extends past their free edge. The nail matrix forms the floor of the proximal nail fold and is a thick epithelium with no granular layer. There are not many studies documenting variations in nail and the nail unit between races. The nail matrix of Caucasians contains sparse, poorly developed melanocytes. In contrast, the distal matrix of people of color is thought to contain more active melanocytes than Caucasian subjects [56]. The number of active melanocytes is also much greater in distal than in proximal matrix. A study by Seaborg and Bodurtha who measured the nails in 48 healthy infants showed that nail area was significantly different among races only for the first fingernail [57].

Conclusion

The development of the skin and its appendages is a complex process requiring interplay of many factors. Although viable after the second trimester of gestation, the skin continues to mature after birth, with modifications seen throughout childhood and adult life, dependent on both internal and environmental factors. Although differences have been elucidated between the different races, further research is required to further delineate the major variations in racial skin.

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Developmental Biology of Black Skin, Hair, and Nails

2

Nikki Tang, Candrice Heath, and Nanette B. Silverberg

Abstract

Black children are children from Africa, the Caribbean, and Latin America whose ancestry is partially or fully Black African. Children who are black have large and active melanosomes producing eumelanin and providing an intrinsic sun protection to the skin, yielding a Fitzpatrick Skin Type of IV–VI. The skin tone is accompanied by curled hair of lesser density and reduced oil distribution along the follicles as well as hyperactive and plumper fibroblasts. This chapter highlights the biological basis of skin tone in children who are of Black descent, with a focus toward clinical correlation with disease states and susceptibility in the Black population.

Keywords

Black skin • Hair • Nails • Africa • Caribbean • Latin America • Fitzpatrick skin type • Melanosomes • Eumelanin

Introduction

- **Black children are children of African ancestry, with matrilineages dating back to 200,000 years ago.**
- **The development of skin pigmentation in black children is felt to have derived from a genetic selection process favoring ultraviolet radiation protection among other valuable features of darker skin.**

Approximately 200,000 years ago, modern day humans first appeared in Eastern Africa. Since then, genetic analyses identified new matrilineages approximately 40,000–80,000 years ago as the Homo sapiens dispersed out of Africa to Eurasia and then 15,000–30,000 years ago to the Americas [1].

Questions about what our ancestors looked like invariably lead to questions about the wide diversity of skin pigmentation. For example, "Black" skin spans a wide range of color and comprises not only Africans and people of African descent, but also African Americans, Caribbean Americans, and Latin Americans. There have been numerous explanations for skin of color. Consistent in these theories is that differences in skin color developed with a strong influence from natural selection and genetic mutations as the first Homo sapiens migrated out of Africa from a climate with consistently high UVR and daytime temperatures into climates with more seasonal variations and lower UVR and daytime temperatures. The ability to adapt to different conditions in this way genetically and phenotypically over centuries has been very important to human survival. While skin pigmentation has a definitive correlation with latitude [2–4], the UV minimal erythemal dose (UVMED) is the environmental factor most strongly correlated with skin pigmentation when measured by skin reflectance [5]. Nearer the equator where UVR is the highest, natural selection favored evolution of darker skin. Several major hypotheses have arisen to explain this evolutionary phenomenon: (1) Protection from sunburn and skin cancer; (2) Greater camouflage in forest environments [6]; (3) Improved permeability barrier function [7], (4) Melanin's antimicrobial

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characteristics [8]; (5) Folate deficiency from UVR-mediated cell division, DNA repair, and melanogenesis [9]; and (6) Thermoregulation.

A discussion of the origins of dark skin should include that of its opposite: the development of fairer skin. The main theory that complements the positive correlation of skin pigmentation with the amount of UVR present is the vitamin D theory, which postulates that lighter skin color evolved in humans migrating from the equator to higher latitudes in order to allow for adequate production of vitamin D. The amount of UVB light needed to generate vitamin D in dark skin is six times as much as in fair skin [10]. It is well known that vitamin D deficiency has many effects on bone health including rickets and osteomalacia and it may also contribute to cardiovascular disease [11], cancer risk, infection, autoimmune disease, and fertility [12]. Yuen and Jablonski argue that effects such as these would affect viability of the young, survival throughout life, fecundity, selection, and longevity [13]; one exception to this would be the Arctic Inuits, whose diet is rich in vitamin D-rich fish oils. Other notable theories of skin lightening include sexual selection [14] and genetic drift [15].

Melanocyte Biology

- **Melanin is the pigment formed in the melanocyte, but is not the only pigment in skin.**
- **The development of melanin in Black children involves enzymatic favoring of eumelanin production as well as larger melanosomes.**

Skin, hair, and eye color is determined by the amount and type of melanin present. Synthesis of this organic polymer takes place in melanocytes located in the basal layer of the epidermis, hair bulb, and iris. The enzyme tyrosinase is the key enzyme overseeing tyrosine's hydroxylation to dihydroxyphenylalanine (dopa), followed by oxidation to dopaquinone. All of this takes place in lysosome-like organelles, melanosomes. Dopaquinone can then proceed down biochemical pathways to either the dark brown/black insoluble DHI (5, 6-dihydroxyindole)-eumelanin (in the absence of cysteine), light brown/alkali-soluble, DHICA (5,6-dihydroxyindole-2-carboxylic acid)-eumelanin (in the absence of cysteine), or red/yellow pheomelanin (in the presence of cysteine) [16]. Following this, melanosomes are secreted into keratinocytes and melanosomes are transported to the epidermal surface [17].

Melanocyte density can differ between body parts, with the highest densities in the forehead, cheeks, and genital areas; however, melanocyte size, shape, and population density are similar between races with the ratio of keratinocytes to melanocytes in the epidermis staying relatively stable at 36:1 (Table 2.1) [18]. The key factors affecting skin pigmentation then are the amount and type of melanin as well as the size and distribution of melanosomes. Dark skin has more DHI-eumelanin and lighter skin has more light-brown DHICA-eumelanin and yellow/red pheomelanins [19]. Furthermore, melanosomes in dark skin are larger and found in single bodies whereas light skin has smaller melanosomes that are clustered together (Table 2.1) [20]. The most widely used scale of skin phototype, the Fitzpatrick scale, was developed in 1975 and initially included skin types I–IV (moving from light, always burns to dark, never burns), but was modified in 1988 to include darker skin types V and VI. This further delineates the cutaneous photoresponse of the darkest patients with type VI skin often being at the greatest risk for dyspigmentation (e.g., hypopigmentation from hair removal laser).

Table 2.1 Ultrastructural differences in melanocyte distribution and melanosome packaging by race and ethnicity

Race	Pigmentary differences
Black (in the USA: African American or Afro Caribbean)	Large (Stage IV) melanosomes Eumelanin constitutes majority of pigment production Closely packed doublet or singlet melanosomes, rare aggregates[a] Larger melanophages (may account in part for greater incidence of melasma and erythema dyschromicum perstans) UV filtration is in the malpighian layer
Caucasian	Small, aggregated melanosomes Pheomelanin Few small melanophages UV filtration in the stratum corneum

[a]Taylor SC. Skin of color: biology, structure, function, and implications for dermatologic disease. J Am Acad Dermatol. 2002; 46(2 Suppl):S41–62

Genetics of Pigmentation

- **Pigmentation is polygenic with contribution from many types of genes ranging from melanin production, distribution, and dispersion genes to melanoblast migration genes.**
- **Alteration in pigmentation genes produces pigmentary alterations ranging from mild skin tone alterations to complete absence of melanin production.**

Pigmentation is polygenic with many different types of genes contributing to the formation of skin tone. Over the last century, many of the studies that discovered genes controlling skin color were investigating pigmentation disorders in humans and animal models. For example, in mice there are greater than 100 genes known to contribute to over 800 phenotypic alleles [21]. With the sequencing of the

Table 2.2 Genes that contribute to pigmentation

Type	Gene	Associated conditions
Tyrosinase enzyme complex	TYR	Oculocutaneous albinism type I/amelanotic melanoma/vitiligo
	TRP1	Oculocutaneous albinism type 3/vitiligo
Melanosomal proteins	MATP	Oculocutaneous albinism type 4
	P gene	Oculocutaneous albinism type 2
	PMEL/SILV	Juvenile xanthogranuloma/melanoma
	SLC24A5	OCA6/Loeys Dietz/patent ductus arteriosus
Regulators of melanin synthesis	MC1R/Alpha-MSH	Melanogenesis/eumelanin production/Skin Cancers
	ASIP	Hair pigmentation; skin cancers
	ATRN	Radioulnar synostosis
Transcription factors of melanin production	PAX3	Waardenburg syndrome, alveolar rhabdomyosarcoma
	MITF	Waardenburg syndrome, types 2 and 2a
	SOX10	Waardenburg syndrome, type 4/Nodular melanoma
Melanosomal transport proteins	MYO5A	Griscelli syndrome, types I and III; Elejalde syndrome
	MYO7A	Usher syndrome Ib
	RAB27A	Griscelli syndrome, type II
Melanosomal construction/protein routing	CHS1	Chediak–Higashi syndrome
	HPS1-6	Hermansky–Pudlak syndrome
Developmental ligands controlling melanoblast migration and differentiation	EDN3	Hirschsprung syndrome/Waardenburg's syndrome
	KITLG	Familial progressive hyperpigmentation
Developmental receptors controlling melanoblast migration and differentiation	KIT	Piebaldism and urticaria pigmentosum/mastocytosis

human genome just over a decade ago, there has been an explosion of new knowledge in this area from studies including comparative genomic and specific allele association studies. Single nucleotide polymorphisms (SNPs) have also been identified in genome-wide association studies that have allowed illumination of genetic variants associated with human pigmentation of the skin, eye, and hair [22]. The most commonly studied genes, TRY, TRP1, P, MATP, MC1R, ASIP, SLC24A5, and MATP, will be described briefly.

The TYR gene encodes for tyrosinase, a copper-dependent enzyme responsible for catalyzing melanin. This gene is mutated in oculocutaneous albinism type 1, with complete or partial loss of gene function (types Ia and Ib, respectively). At present, there are over 100 mutations associated with albinism or skin color dilution [23]. Also contributing to the tyrosinase enzyme complex is TRP1, mutations in which result in oculocutaneous albinism type 3. In individuals of sub-Saharan African heritage with oculocutaneous albinism type 2, mutations in the P gene cause a defective melanocytic transporter protein resulting in light blond or yellow hair, vision problems, and white skin. MATP is a membrane-associated transporter protein associated with OCA type 4 that shows strong selection in European populations.

Another widely studied pigmentation gene is the melanocortin 1 receptor (MC1R, also called alpha melanocyte stimulating hormone) gene, which codes for a G protein-coupled receptor important in melanocytic switching between production of eumelanin and pheomelanin. Loss-of-function mutations of MC1R have been associated with people with red hair and fair skin (autologous to an autosomal recessive trait), but are also seen in up to 30 % of the population and may play a role in lighter skin color [24]. European populations show a higher sequencing diversity of MC1R, which reflects neutral expectations of selection under relaxation of functional constraints especially when compared to sub-Saharan African and other dark-skinned populations, which are thought to be under stronger functional constraints and show a lack of sequencing diversity [25, 26].

ASIP, the agouti signaling protein, acts antagonistically at the MC1R receptor to inhibit the production of both eumelanin and pheomelanin; and the 8818G allele is strongly associated with dark hair, brown eyes, and dark skin [27, 28]. Lastly, a gene contributing to the "lightening" of skin is the "golden" gene (SLC24A5) coding for a melanosomal cation exchanger and responsible for up to 25–38 % of the difference between the European versus African melanin index of the skin [29]. Other genes implicated in pigmentation are seen in the Table 2.2 (Fig. 2.1).

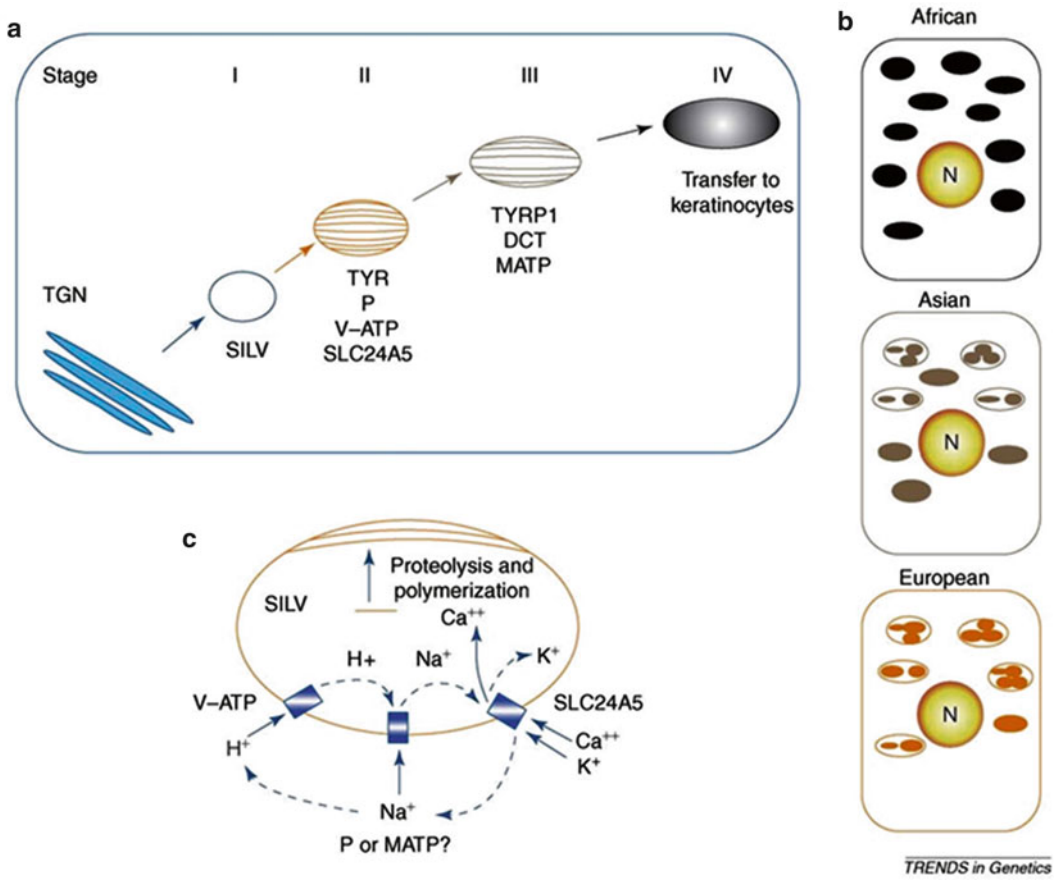

Fig. 2.1 Melanosome formation and the role of ion transport in their maturation. (**a**) The four-stage model of melanosome formation is shown together with key proteins that are necessary for each step of maturation before melanosomes are passed to keratinocytes. (**b**) Keratinocyte distribution of melanosomes in ethnic populations, note that the melanosomes often form a cap surrounding the nucleus that might have a role in photoprotection. (**c**) A model for ion transport that is essential to melanosome function. The coupling of H^+, Na^+ exchange by the V–ATP complex, with possible involvement of the P or MATP proteins, enables SLC24A5 (also known as NCKX5) to transport K^+, Ca^{2+} ions into the melanosome. Ca^{2+} might have an essential role in activating the proteolytic cleavage of SILV, which polymerizes to form the melanosomal matrix copied with permission from Sturm R. 2006 [30]

Hair

- **Hair type can be categorized by shape of hair in cross section, curvature or lack thereof of the follicle, density of the hairs, and content of sulfur in the hairs.**
- **Hair type may have racial or ethnic association for the general public.**
- **Hair in Black patients can be more susceptible to illness due to reduced density, less elastic anchorage, and cultural styling practices.**

In the literature, research often focuses on grouping hair textures into African, Caucasian, or Asian. These distinctions, though heavily studied and helpful, do not take into account the multitude of the world's population that may not fall into one of these categories due to inter- and inner-group variation of hair types. A study of 1,442 people from 18 countries revealed 8 different hair types [31]. Hardy classified hair types without incorporating race, but the classifications have not been widely used [32]. Khumalo suggests that race has been used as a proxy for describing hair forms, despite obvious inter-racial variation [33, 34].

Khumalo expressed the need for an easy to use classification of hair forms that is inclusive of multiple hair types. Despite this desire, the most commonly used terminology to describe hair types still utilizes racial classifications.

When cross sections of hair are viewed, Asian hair is round. Caucasian hair is thinner and more elliptical than Asian hair. African hair is often textured, is coiled, and is the most elliptical [35]. On cross section, Black hairs will be flattened. Textured hair and dryness of the scalp and hairs are common in Black hair, due to reduced sebum production/distribution along the hair shaft and reduced water content in the hairs. The hair follicle is expected to be helical or curved, with limited elastic fiber anchorage. Lower hair density is noted in Black

patients (0.6 follicular units per square mm vs. 1 follicular unit per square meter in Asians and Caucasians) [36–38].

It is well known that African textured hair may be straightened permanently with chemical relaxers and temporarily with heat, with side effects ranging from frizziness to follicular destruction [39]. Close observation has revealed that the African texture is also noted to change during certain types of illnesses and states of health such as AIDS, rheumatoid arthritis, systemic lupus erythematosus, pulmonary tuberculosis with cachexia, and Behçet's disease, especially those with anemia of chronic illness, high erythrocyte sedimentation rate, and mild hypocalcemia [40].

In infants, the hair whorl may be hard to note in Black children due to the curl of the hair compounded by the popularity of shaven hairstyles. Microscopy of hair in Black children demonstrates discrete hair packets and curled hairs.

Follicular prominence can be noted in Black adolescents resulting in a light halo near each sebaceous hair follicle of the face. Follicular inflammation is more common in Black children with consequently greater amounts of follicular eczema and folliculocentric allergic contact dermatitis.

Some studies have suggested that sebaceous glands are larger in Blacks than in Caucasians, and therefore, sebum, the oil produced by sebaceous glands, has greater lipid content [41, 42]. This may possibly allow for greater bacterial and yeast overgrowth.

Dermal

- **Fibroblasts are larger in the dermis of Black children contributing to the increased incidence of keloidal lesions in this racial group.**
- **Elastic tissue anchorage of the hair follicle is reduced resulting in greater damage with traction-based hairstyles.**

Skin thickness is the same in Blacks and Whites [43], despite the compact nature of the stratum corneum in Blacks [44]. Fibroblasts in Black skin are larger than those in White skin [45]. Elastic tissue anchorage of the hair follicle is reduced in Black patients resulting in greater risk of traction-induced damage.

Keloids result from unbalanced extracellular matrix production and degradation [46]. Hyperactive fibroblasts contribute to keloid formation and are influenced by transforming growth factor beta, epidermal growth factor, mast cells, and decreased collagenase activity [47–49].

Keloid development is influenced by many factors including genetic susceptibility including racial prevalence amongst Blacks, Asians, and Hispanics, family linkage, and HLA associations and corroborated by twin studies. Environmental contributory factors include hormones, wound tension, infection, and foreign body granulomas. Another factor that authors note in practice is the comorbidity of nickel contact allergy, often induced by piercing, as a trigger of keloids secondary to piercing.

Other Considerations

- **Genetic differences in metabolism and skin structure can affect response to medications.**
- **Awareness of G6PD deficiency, an X-linked recessive enzymatic defect, is needed for practitioners who prescribe dapsone and antimalarial medications, due to the risk of severe hemolysis.**
- **The role of environment on development of skin diseases is especially contributory in the development of atopic dermatitis in developed countries.**

Some dermatologic diseases affecting patients with skin of color have been linked to genetic propensity. For example, sarcoid, is associated with specific HLA types in Black patients [50, 51].

Vitiligo is more prominent in children of color, but despite this, no specific linkage genes to race have been identified in Black children. Vitiligo genetics is actually polygenic and multifactorial [52]. On the other hand, OCA2, an autosomal recessive albinism, has a specific gene defect and is the most prevalent autosomal recessive disease among South African Blacks, P protein is defective in OCA2 leading to abnormal tyrosinase enzyme function and defective melanin production [52].

Keloids have long been observed to occur more frequently in skin of color populations, especially in those of African descent. Studies now suggest that certain environmental triggers may spur keloid formation in those who are genetically susceptible [53].

Other pertinent genetically common illnesses in patients of Black or African descent include G6PD deficiency, an X-linked recessive enzymatic defect that affects metabolism of medications such as dapsone and hydroxychloroquine and can result in severe hemolysis with drug administration of these agents. Male patients should be suspected most, but all black patients should be screened prior to usage of these agents as female patients may be homozygous or have low expression based on lyonization.

Sickle cell anemia can confer susceptibility to bacterial infection (e.g., *Streptococcus*) [54] and is associated with severe hemolysis requiring hospitalization for transfusion in children with G6PD deficiency. Sickle cell carriers may be less prone to malaria, generating the hypothesis as to why sickle cell carriage and disease are more common in patients of African descent [55].

Type II diabetes mellitus is associated with acanthosis nigricans, skin tags, candidal infections, and poor wound healing. In the USA, Black, Native American/Inuit, and Mexican American children are at increased risk. Signs of insulin resistance, especially acanthosis nigricans, are noted

in pre-teen years with disease becoming full blown in some cases by the mid-teen years [56, 57].

Black children also have specific reduction in the formation of infantile hemangiomas [58] and lifetime risk of skin cancers [59] (lifetime risk is lower). Collagen vascular diseases are more common from birth, i.e., neonatal lupus through childhood/adolescence when Black children may develop the first features of lupus erythematosus, with specifically increased risk of nephritis [60]. More than 60 % of patients under the age of 20 years with systemic lupus erythematosus will be Black [61].

The effect of the environment/country/place of birth on the disease incidence cannot be ignored, e.g., atopic dermatitis being more common in Afro-caribbeans in London, but relatively less common in Africans on the continent, etc. In addition, differences in the pattern of skin disease exist between races. Henderson et al. found that more than 60 % of all pediatric patients seen at their dermatology clinic had diagnoses of acne (28.6 %), dermatitis (19.4 %), and warts (16.2 %) [62]. But when the patients were further stratified, they found that African-American pediatric patients in their study were most commonly seen for dermatitis (29.0 %), acne (27.5 %), and dermatophytosis (10.2 %), whereas Caucasian children were most commonly seen for acne (29.9 %), warts (22.6 %), and dermatitis (13.1 %).

Another study of both adults and children at our Skin of Color Clinic at St. Luke's Roosevelt Hospital in New York City found similarities between common diagnoses in Black and Caucasian skin. However, dyschromia and alopecia were two conditions commonly seen in black patients that were not even in the top ten diagnoses of Caucasian patients [63]. The most common diagnoses in African-American patients were acne, dyschromia, contact dermatitis/other eczema of unspecified cause, alopecia, and seborrheic dermatitis. In Caucasian patients, the most common diagnoses were acne, lesion of unspecified behavior, benign neoplasm of skin of trunk, contact dermatitis/other eczema of unspecified cause, and psoriasis.

Those studies, along with others from around the world, show similar patterns comparing disease incidence in skin of color to Caucasian skin, but modern travel has enabled entire groups of people to be mobile and migrate globally. While there are numerous genetically determined biological factors discussed earlier in the chapter that are responsible for the characteristics of skin of color and resultant epidemiological differences of diseases between races, environment also plays a role in disease incidence.

One representation of environment playing a role in disease incidence is examining atopic dermatitis and eczema. London-born Black Caribbean children were thought to have an increased risk of atopic dermatitis [64] and were also thought to be more likely to develop atopic eczema when compared to their counterparts in Kingston, Jamaica [65]. Another London study of a Black population showed the most frequent dermatoses in their pediatric population were atopic eczema (36.5 %) and tinea capitis (26.5 %), whereas adults were most commonly diagnosed with acneiform eruptions (27.4 %) and eczema (9.6 %) [66]. Compare this to a Jamaican study, which did not separate their data between adults and children, that identified the most common skin diseases as acne vulgaris (29.21 %), seborrheic eczema (22.02 %), pigmentary disorders (16.56 %), and atopic eczema (6.1 %) [67]. The frequency of dermatitis and atopic eczema in Black patients found in the Western countries was greater than those found in less developed countries, with theories including increased hygiene in countries that are developed (e.g., varicella vaccination) [68], indoor heating, and cultural factors such as washing [69].

Furthermore, the different rates of atopic eczema between countries can be explained at least partially by their natural environment/climates and not only by immunogenic theory. For example, eczema is known to be triggered by skin dryness, so comparing the rates of atopic dermatitis (13.8 %) and contact dermatitis (5.8 %) seen in the more tropical Nigeria [70] to those rates of eczema seen in the drier and semi-arid weather of South Africa (32.7 %) [71] would support this. That environmental factors are important in disease expression was also suggested by the authors of a multi-country cross-sectional study, which showed symptoms of atopic eczema with widely varying rates of prevalence both within and between countries with similar ethnic groups [72].

Conclusion

Black children today, and their skin, reflect the culmination of 200,000 years of environmental exposure and genetic selection. Understanding of these contributory factors is crucial in the appreciation of Black skin.

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Pigmentary Development of East Asian Skin

3

Kin Fon Leong

Abstract

East Asians have a large range of skin types and different cultural beliefs.

Knowledge about normal variations in skin color and common pigmentary disorders among East Asians is essential to avoid overdiagnosis.

Although most pigmentation disorders are benign or non specific, some pigmentation disorders present cosmetic or psychological challenges to the patient, necessitating systematic evaluation and treatment.

Pigmentary disorders are broadly classified into three groups:

1. Hypopigmentation or depigmentation
2. Hyperpigmentation
3. Mixed

These disorders can be further subcategorized based on their age of onset, pattern and distribution. i.e., Hypomelanosis of Ito is categorized under early onset patterned hypopigmentary disorder.

Keywords

East Asian • Skin • Color • Melanin • Pigment • Melanocytes

Introduction

Indent Asia is the world's most populated continent, with over four billion people. About half of them reside in East Asia (including China, Japan, Taiwan, and Korea) and Southeast Asia (including Indonesia, Thailand, Myanmar, Vietnam, Laos, Cambodia, Philippines, East Timor, Singapore, and Malaysia). East Asians have different cultural backgrounds and their skin types are Fitzpatrick skin types II–IV.

A study that involved 404 Chinese females living in different cities has concluded that the skin types are principally type III (more than 70 %), and then type II (14.7 %) and type IV (14.2 %) [1]. Variations in skin color are evolutional and are an adaptation response of humans to environmental conditions, especially ultraviolet radiation.

The skin the most visible aspect of the human appearance and its color is one of its most variable features. Pigmentary disorders are more visible in Asian skin, and are of great cosmetic concern. Certain pigmentary disorders are more frequent among East Asians; these include Nevus of Ota, Mongolian blue spots, reticulate acropigmentation of Kitamura, post-inflammatory dyspigmentation, etc.

Physiology and Embryology of Skin Color

Normal skin color is influenced mainly by:

1. Melanin pigment
2. Degree of vascularity related to oxygenated hemoglobin (red) in capillaries and deoxygenated hemoglobin (purplish) in venules

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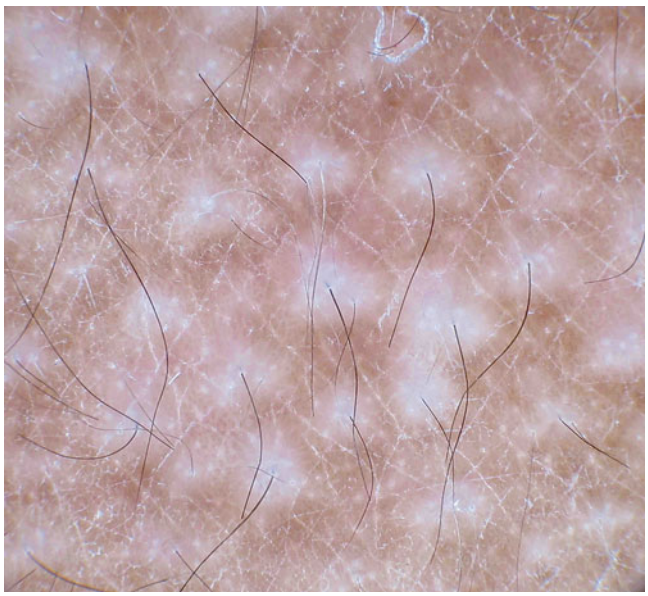

Fig. 3.1 Perifollicular hypopigmentation is due to accumulated keratin at follicular orifices

3. Carotene (yellow to orange)
4. Thickness of stratum corneum (Fig. 3.1)

Melanin is the principal pigment present in the skin that looks darker the more concentrated it is. It can be found in two different colors: yellow/red (pheomelanin) and brown/black (eumelanin). Differences in skin pigmentation among individuals are related to the concentration and ratio between eumelanin and pheomelanin, as well as the distribution of melanin in the basal layer and epidermis, rather than the number of melanocytes as its number is relatively constant in different races. In most East Asians, Indians, and Africans, the predominant pigment is eumelanin, and among the fair red-headed Caucasians, the predominant pigment is pheomelanin.

Besides the melanin concentration and ratio, its location at the epidermis or dermis also affects the final skin color due to Tyndall effect. Longer wavelengths such as red penetrate deeper and are absorbed by melanin. Since blue does not penetrate so deeply it is not absorbed and is reflected back, which is why dermal pigment appears blue in dermal melanocytosis.

Melanocytes are the key player in most pigmentary disorders. They are dendritic cells that are derived from melanoblasts, which originate from the neural crest. During embryogenesis, progenitor melanoblasts migrate between mesodermal and ectodermal layers to reach their final destinations in the epidermis and hair follicular bulbs, as well as the inner ear cochlea, choroids, ciliary body, and iris [2]. Any disruption of the migration of melanoblasts from the neural crest to the basal layer of the epidermis, lack or excess in production of melanin, and transfer of melanosomes from melanocytes to keratinocytes in the epidermis will result in pigmentary defects with variable degrees of extracutaneous involvement. Therefore, the eyes and hearing in addition to the skin and hair are defective in some genetic pigmentary disorders, e.g., Waardenburg syndrome. Melanin biosynthesis is primarily regulated by tyrosinase, a copper-dependent enzyme that converts tyrosine to dihydroxyphenylalanine (DOPA). It is the most important rate-limiting enzyme in melanogenesis.

Normal Variants in Skin Pigmentation

Knowledge about normal variations in skin color is important for us to distinguish them from other abnormal skin discolorations to avoid overdiagnosis. Below are some of the common variants among East Asian children.

1. **Pigmentary demarcation lines (PDL)**
   Pigmentary demarcation lines (PDL), also known as Futcher's lines or Voight's lines, were first described by the Viennese anatomist Christian A. Voight.

   In all races, the dorsal skin surfaces have relatively higher pigmentation compared to the ventral surfaces. There are lines of demarcation (Type A–E) between dorsal and ventral skin surfaces (Figs. 3.2, 3.3, and 3.4) [3]. These demarcation lines are bilateral symmetrical/midline and present from infancy and persist throughout adulthood.

   Knowledge about them is essential; i.e., Type C and E pigmentary demarcation lines may be confused with nevus depigmentosus.
2. **Perifollicular hypopigmentation** (see Fig. 3.1)

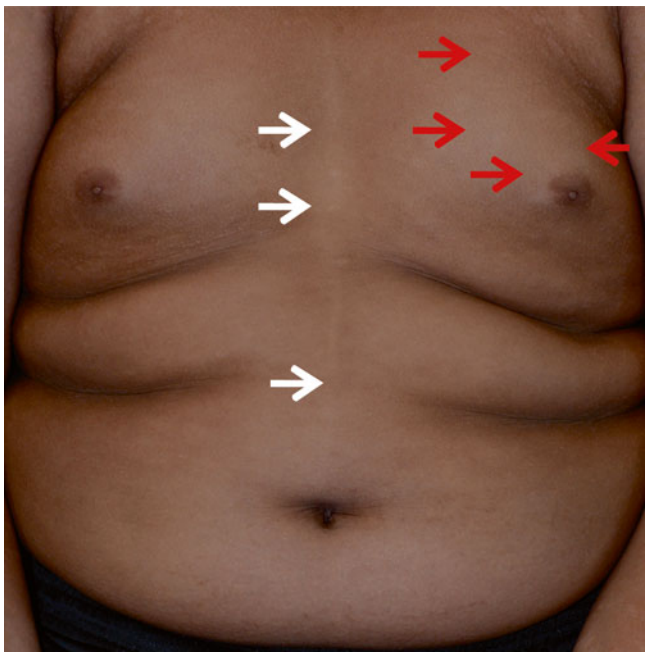

Fig. 3.2 Type C and type E pigment demarcation lines. Type C—hypopigmented lines present as paired median or paramedian lines on the chest with midline abdominal extension (*white arrow*). Type E—Bilateral chest markings (hypopigmented macules and patches) in a zone that runs from the mid third of the clavicle to the periareolar skin (*red arrow*)

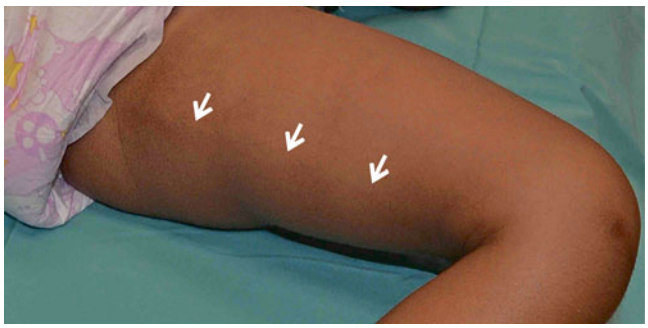

Fig. 3.3 Type B pigment demarcation lines. A *curved line* on the posteromedial thigh that extends from perineum to popliteal fossa (*white arrow*)

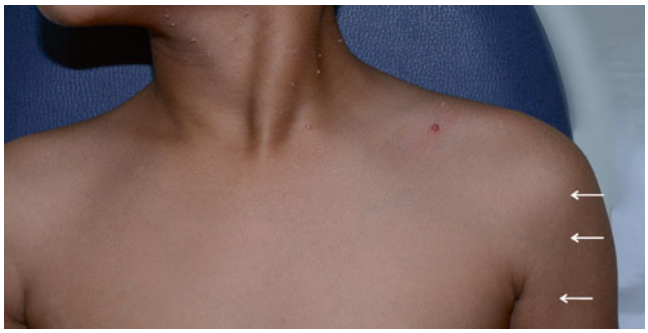

Fig. 3.4 Type A pigment demarcation lines. A *vertical line* along the anterolateral portion of upper arm that may extend into the pectoral region (*white arrow*)

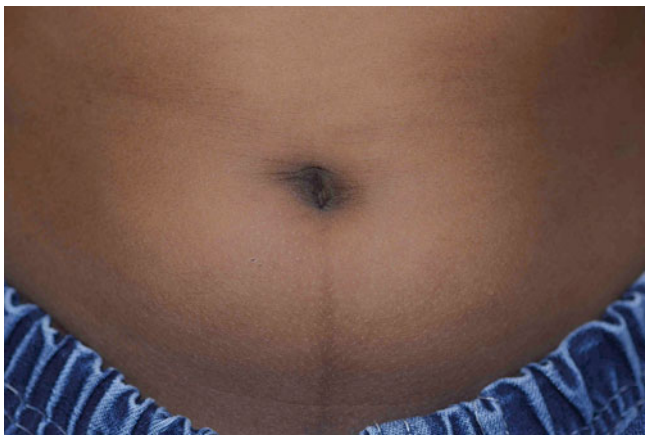

Fig. 3.5 Linea nigra. It is a fairly common finding in children especially those with darker skin types

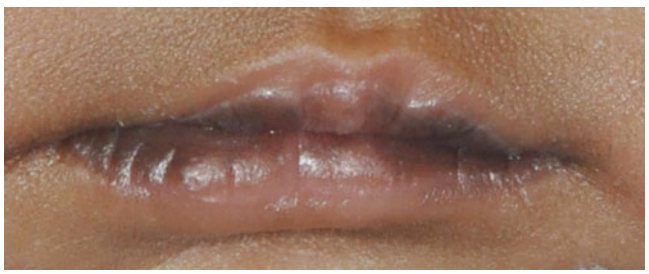

Fig. 3.6 Diffuse hyperpigmentation of upper and lower lips

3. **Linea nigra** (Fig. 3.5)
4. **Lip hyperpigmentation** (Fig. 3.6)

Other darkly pigmented areas that are regarded as normal include the genital area, the elbows and the knees, the knuckles, and in many, a mild degree of infraorbital pigmentation.

Classification of Pigmentary Disorders in Children

Although most pigmentation disorders are benign or nonspecific, some pigmentary disorders present cosmetic or psychological challenges to the patient, necessitating systematic evaluation and treatment. Others may be indicators of underlying genetic disorders with systemic involvement.

Pigmentary disorders are first broadly classified into three groups (Fig. 3.7):

1. Hypo- or depigmentation (Figs. 3.8 and 3.9)
2. Hyperpigmentation (Figs. 3.10, 3.11, and 3.12)
3. Mixed hypo- and hyperpigmentation (Fig. 3.13)

Hypopigmentation disorders in children can be due to a wide variety of congenital and acquired diseases (Table 3.1). Since their underlying causes are heterogeneous and histological examination of the skin alone is rarely diagnostic, a systematic clinical approach is essential (Fig. 3.14).

The disorders are usually classified based on the age of onset into early and later childhood, and in each category they are subdivided into localized and generalized hypopigmentation. Other clinical findings, listed in Table 3.2, are helpful to distinguish the disorders further.

Similarly, hyperpigmentation disorders in children can be due to many causes (Table 3.3). Localized or patterned hyperpigmentation of early onset is frequently developmental or hereditary in origin. However, pigmented lesions may also be acquired later in childhood following inflammatory dermatoses especially among Asian children with skin types IV to VI.

Epidermal melanosis is usually brown to black in color and is enhanced with a Wood's lamp, whereas dermal melanosis tends to produce blue-gray lesions and is not enhanced by Wood's light. Some disorders, such as melasma in adults, may have dermal and epidermal changes and can be classified as mixed.

The dyschromatoses are a group of pigmentary disorders characterized by a combination of hyper- and hypopigmentation without atrophy or telangiectasia as seen in poikiloderma.

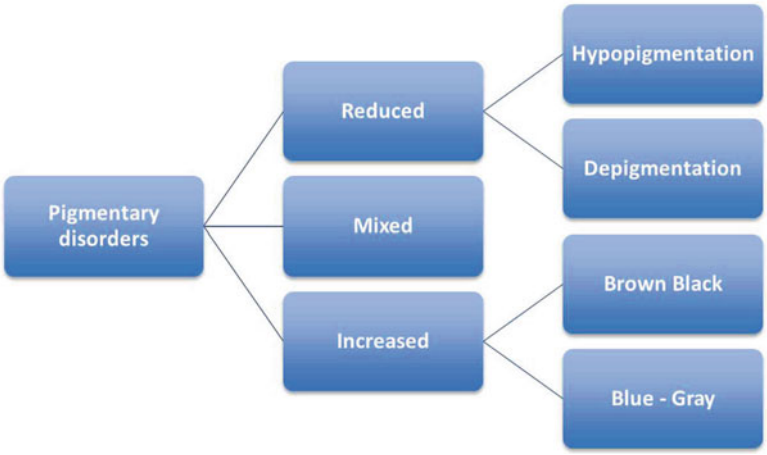

Fig. 3.7 Classification of pigmentary disorders in children

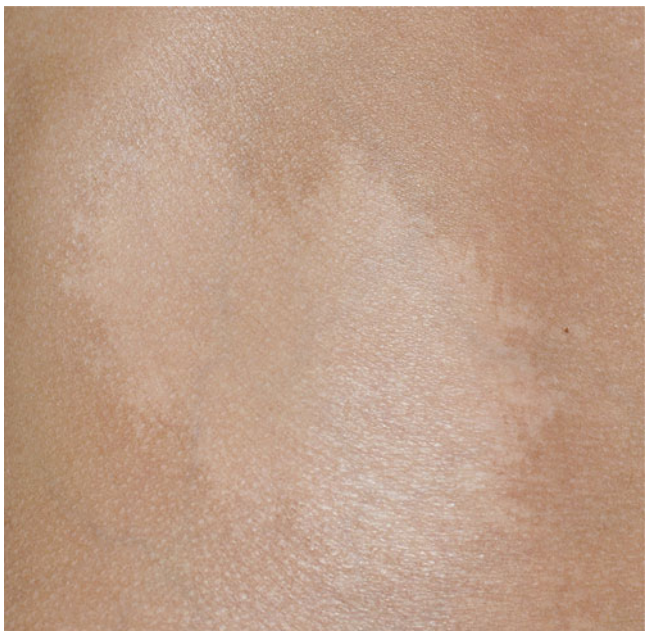

Fig. 3.8 Hypopigmented patch

Fig. 3.9 Depigmented patch

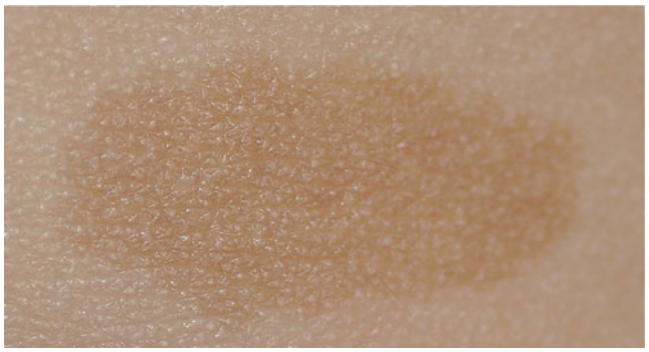

Fig. 3.10 Light brownish patch

Group A-1: Early-Onset Hypopigmentary Disorder

Nevus Depigmentosus

Introduction

Nevus depigmentosus (ND) is defined as a congenital non-progressive hypopigmented macule or patch that was first reported by Lesser in 1884. It is caused by aberrant transfer of melanosomes to the keratinocytes.

Clinical Features

Morphology

Nevus depigmentosus is a misnomer as the area of involvement is actually hypopigmented and not depigmented patch. It has an irregular but well-defined margin. The shape of the lesion is variable and may be round or rectangular. Its surface is smooth and non-scaly (Fig. 3.15).

Distribution and Pattern

It may occur at most body sites, but the most common site is the trunk [4]. Occasionally, a patient will have a unilateral segmental lesion that follows the lines of Blaschko.

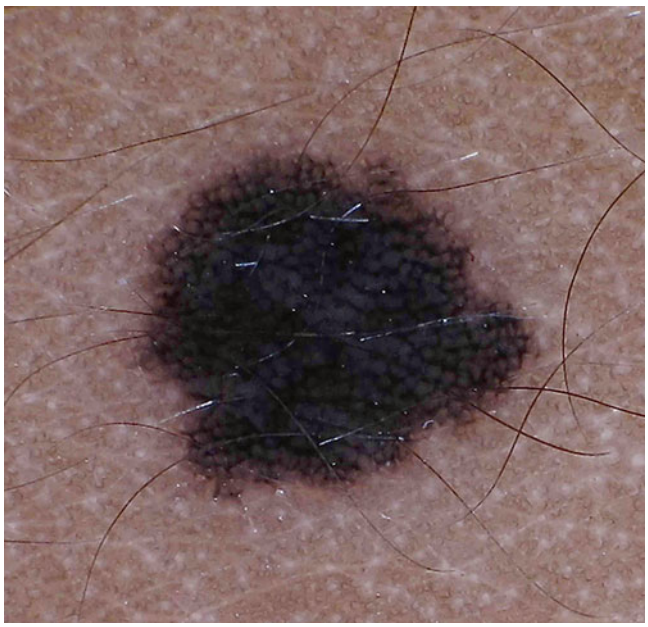

Fig. 3.11 Black macule

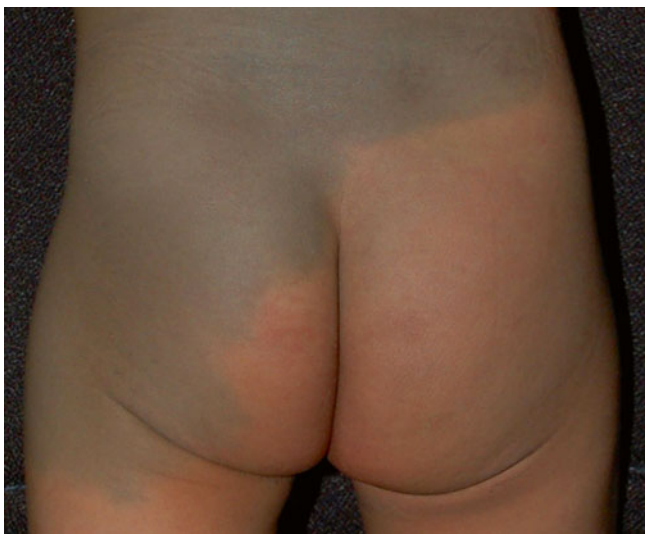

Fig. 3.12 Blue-gray patch

Due to clinical overlap among some of these lesions with hypomelanosis of Ito, the umbrella term of "nevoid linear hypopigmentation" is used by some clinicians.

Clinical diagnostic criteria for nevus depigmentosus proposed by Coupe in 1976 are:

1. Leukoderma present at birth or onset early in life
2. No alteration in distribution of leukoderma throughout life
3. No alteration in texture, or change of sensation, in the affected area
4. No hyperpigmented border around the achromic area

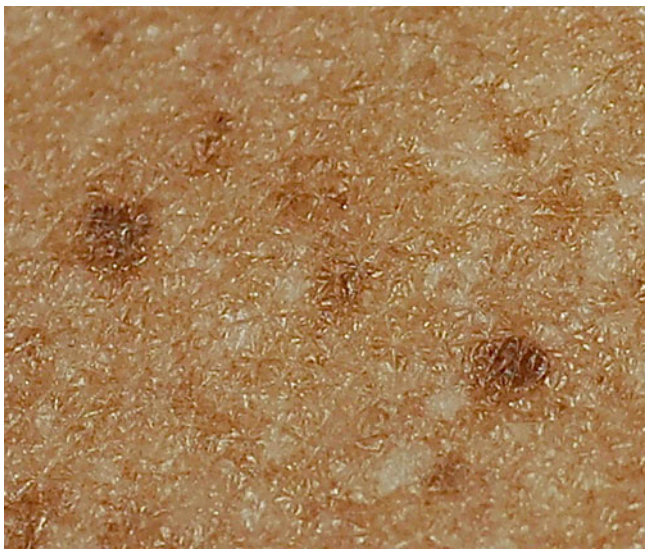

Fig. 3.13 Mixed hypo- and hyperpigmented macules

Table 3.1 Causes of hypopigmentation in children

Hypopigmentary disorders in children	
Group A (Localized with early onset)	**Group A-1: Hypopigmented** 1. Nevus depigmentosus[a] 2. Hypomelanosis of Ito[a] 3. Nevus anemicus 4. Tuberous sclerosis 5. Post inflammatory hypopigmentation[a] **Group A-2: Depigmented** 1. Piebaldism 2. Waardenburg syndrome 3. Vitiligo[a]
Group B (Generalized and early onset)	**Group B-1: Skin, hair and eyes** 1. Oculocutaneous albinism 2. Chediak–Higashi syndrome 3. Hermansky–Pudlak syndrome 4. Prader Willi and Angelman syndrome 5. Metabolic disorders (a) Phenylketonuria (b) Histidinemia (c) Homocystinuria **Group B-2: Skin and hair only** 1. Griscelli syndrome 2. Elejalde syndrome 3. Menkes disease 4. Copper and Selenium deficiency
Group C/D (Late onset localized/ generalized)	**Depigmentated** 1. Vitiligo[b] 2. Post inflammatory leukoderma **Hypopigmentation** 1. Post inflammatory hypopigmentation (a) Eczema or psoriasis (b) Pityriasis lichenoides chronica (c) Lichen striatus (d) Infection 2. Pityriasis alba 3. Hypopigmented mycosis fungoides 4. Morphea 5. Lichen sclerosus et atrophicus (LSEA)

[a]Can present as localized or generalized distribution and pattern
[b]Early onset vitiligo may present during infantile period but not at birth

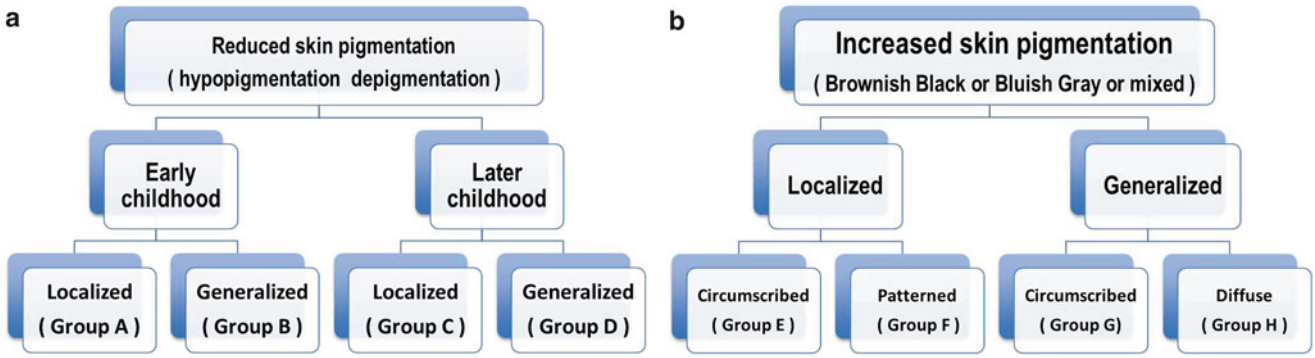

Fig. 3.14 (**a**, **b**) Classification of hypopigmentation and hyperpigmentation in children

Table 3.2 Helpful clinical findings to subcategorize children with hypopigmentation disorder

Helpful clinical findings	
Age of onset	(A) Early onset: At birth to first 2 years of life (B) Late onset: After 2 year-old
Distribution and pattern	(A) Involvement of skin ± hair ± mucous membranes ± eyes (B) Localized Generalized (a) Diffuse (b) Circumscribed (C) Patterned or non-patterned
Morphology	Surface changes 1. Scaly 2. Atrophy 3. Verrucous
Extracutaneous features	Neurological, musculoskeletal, eyes and ears, etc.
Others	Special tests 1. Wood's light 2. Test for skin sensation Family tree to identify the pattern of inheritance

Extracutaneous Findings

It has rarely been reported in association with hemihypertrophy and neurological deficit.

Clinical Course

Nevus depigmentosus is usually present at birth or becomes evident shortly thereafter. Its size increases in proportion to the growth of the child. In Korea, a clinical survey that involved 67 patients with nevus depigmentosus has concluded that the majority (92.5 %) of them present before 3 years of age, but some lesions also appeared later in childhood (7.5 %). Forty patients (59.7 %) had the isolated type of nevus depigmentosus and 27 patients (40.3 %) had the segmental type [5].

Differential Diagnosis

1. Vitiligo
   Cases of late-onset nevus depigmentosus are sometimes misdiagnosed as segmental vitiligo. It is important to distinguish it from childhood vitiligo because they have different prognostic and psychosocial effects. Furthermore, ND is not responsive to topical steroid and phototherapy.
2. Nevus anemicus (NA)
   Nevus anemicus typically presents with an asymptomatic pale macule or patch with irregular margin that has been present since birth and grows with the child. It may be seen in close association with a port-wine stain (Fig. 3.16). It is due to persistent increase in vascular tone, which results in localized vasoconstriction.
   Three simple maneuvers to differentiate NA from others are:
   (a) Under diascopy, the lesion becomes indistinguishable from the blanched surrounding normal tissue
   (b) Wood lamp doesn't accentuate the lesion
   (c) Rubbing causes erythema of the surrounding area but not within the lesion itself.
3. Hypomelanosis of Ito
4. Piebaldism
5. Tuberous sclerosis
6. Post-inflammatory hypopigmentation (Fig. 3.17)

Treatment: Camouflage is helpful if the lesion occurs on cosmetically important areas. Sun protection with clothing and sunscreen is useful to prevent sunburn. Autologous melanocytic transplantation is another option that has given variable results [6].

Hypomelanosis of Ito

Introduction

Hypomelanosis of Ito (HI) is a descriptive term applied to individuals with skin hypopigmentation along the lines of Blaschko. Even though originally described as a purely cutaneous disease by Dr. Ito in 1952, subsequent reports have showed a frequent association with neurological abnormalities leading to frequent characterization as a neurocutaneous disorder. Hypomelanosis of Ito is believed to be due to chromosomal mosaicism and

Table 3.3 Causes of hyperpigmentation and dyschromia in children

Hyperpigmentary disorders in children	
Group E: Localized circumscribed hyperpigmentation (single to few lesions)	**Group E-1: Brown/black** 1. Café au lait macule[a] 2. Congenital melanocytic nevus[a] 3. Segmental pigmentation disorder 4. Nevus spilus 5. Becker's nevus 6. Post inflammatory hyperpigmentation **Group E-2: Blue gray** 1. Mongolian spots 2. Nevus of Ota 3. Nevus of Ito 4. Phakomatosis pigmentovascularis[a] 5. Ashy dermatoses[a]
Group F: Localized patterned hyperpigmentation	1. Epidermal nevus 2. Hyperpigmentation stage of IP 3. Linear and whorled nevoid hypermelanosis 4. X linked chondrodysplasia punctata
Group G: Generalized circumscribed hyperpigmentation (few to multiple)	**Group G-1: Brown/black** 1. Maculopapular cutaneous mastocytosis 2. Multiple lentigines syndrome 3. Post inflammatory hyperpigmentation 4. Transient neonatal pustular melanosis 5. Giant congenital melanocytic nevi with satellite lesions 6. Tinea versicolor 7. Xeroderma pigmentosum (early) **Group G-2: Blue-gray** 1. Ashy dermatoses 2. Phakomatosis pigmentovascularis 3. Generalized fixed drug eruption
Group H: Generalized diffuse hyperpigmentation	**Group H-1: Without skin thickening or hyperkeratosis** 1. Drugs e.g., clofazimine, minocycline 2. Post inflammatory hyperpigmentation 3. Chronic liver failure and renal failure 4. Hemochromatosis **Group H-2: With skin thickening or hyperkeratosis** 1. Congenital ichthyosis 2. Acanthosis nigrican 3. Generalized exfoliative dermatitis
Group I: Dyschromatosis (mixed hypo- and hyperpigmentation	1. Dyschromatosis symmetrica hereditaria 2. Dyschromatosis universalis hereditaria 3. Early xeroderma pigmentosum 4. Chronic arsenic poisoning 5. Dyschromic amyloidosis cutis

[a]Can present as localized or generalized pattern

sporadic mutations. It is not an inherited disorder as the chromosomal defect occurs after conception. Recurrence is uncommon. The specific gene(s) involved has not been confirmed.

Clinical Features

Morphology

Lesions first appear at birth or become apparent within the first 2 years of life as small hypopigmented macules that are arranged in linear, whorls, or streaks. Their surfaces are smooth, non-scaly, and not preceded by inflammation. Wood's lamp examination is helpful for Asians with fair skin and also during the early infantile period as skin pigmentation according to skin type has not been established.

Distribution and Pattern

The hypopigmented macules are arranged along the Blaschko lines (Figs. 3.18 and 3.19)

It may be unilateral or bilateral. Palmoplantar regions, scalp, and mucous membranes are usually not affected.

Extracutaneous Features

Extracutaneous involvement is variable, and includes central nervous system, musculoskeletal, dental, eye, and cardiac abnormalities.

The literature contains reviews, mostly from neurology departments that report rates of hypomelanosis of Ito-associated neurologic abnormalities as high as 75–94 %.

This figure is higher in a pediatric neurology clinic-generated series and when systemic involvement was used as

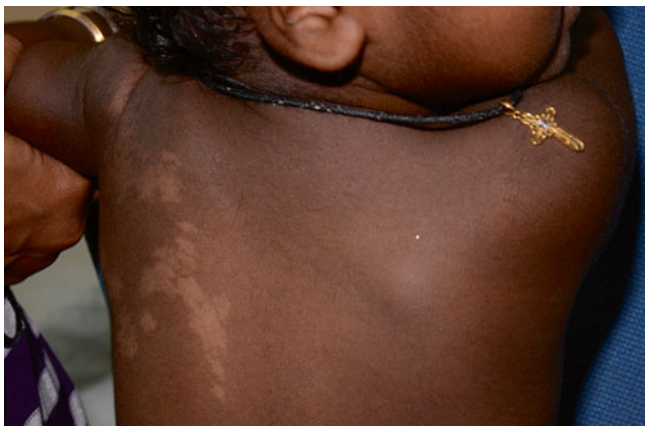

Fig. 3.15 Nevus depigmentosus. A healthy baby girl was noted to have a hypopigmented patch on the left upper back since birth

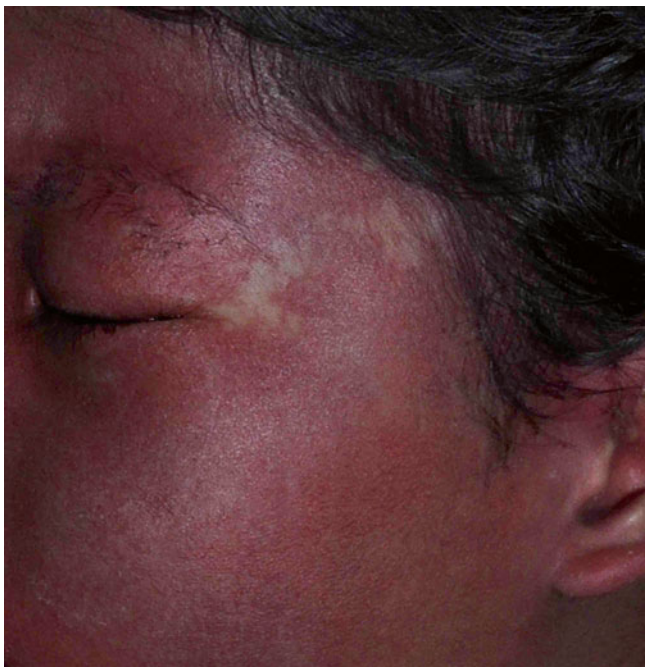

Fig. 3.16 Nevus anemicus. The boy has a congenital pale patch on his left temple with underlying portwine stain

a key diagnostic criterion [7, 8]. More recent groups estimate that the associated anomaly rate is 30–50 %.

Affected children require a careful medical, neurologic, ocular, and musculoskeletal examination and a regular developmental milestones assessment. Further imaging studies are tailored to the clinical findings.

Common findings include seizure, mental retardation, hearing and visual abnormalities, and tooth and musculoskeletal defects.

Diagnosis of Hypomelanosis of Ito

Some authorities advocate stricter criteria for diagnosis, requiring cutaneous involvement of two or more segments plus systemic involvement for definite diagnosis of hypomelanosis of Ito [9]. However, these criteria cannot be considered

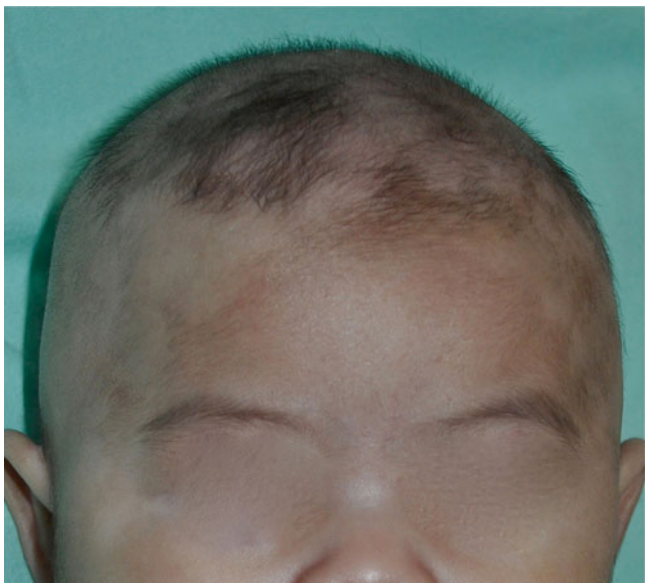

Fig. 3.17 Post-inflammatory hypopigmentation on scalp and hairlines. Noted in a 3-month-old boy secondary to infantile seborrheic dermatitis

to be definitive until the etiology is more clearly understood as there are a lot of clinical overlaps, e.g., systematized nevus depigmentosus. Hence, the distinction between hypomelanosis of Ito and nevus depigmentosus may be artificial.

Hypomelanosis of Ito is a clinical description and not a diagnosis. Practically, nevoid hypopigmentation with or without systemic involvement is probably a better way to approach these skin lesions.

Differential diagnoses are the hypopigmented stage of incontinentia pigmenti, linear whorled nevoid hypermelanosis, Goltz syndrome, and systematized nevus depigmentosus.

Cytogenetic analysis of peripheral blood lymphocytes and skin fibroblasts should be considered in all the children with segmental or linear pigmentary disorders with extracutaneous involvement to look for chromosomal mosaicism.

Treatment

No specific treatment is available. Camouflage is helpful for areas of cosmetic concern.

And sunblock is useful to reduce the pigmentary differences as the lesions will be more obvious with the differential tanning response compared with the surrounding normal skin.

Tuberous Sclerosis Complex

Introduction

The name "tuberous sclerosis" comes from "tubers" (protuberances) and areas of "sclerosis" (hardening) in the cerebral gyri that calcify with age. Tuberous sclerosis complex (TSC) was first recognized by Friedrich Daniel von Recklinghausen in 1862.

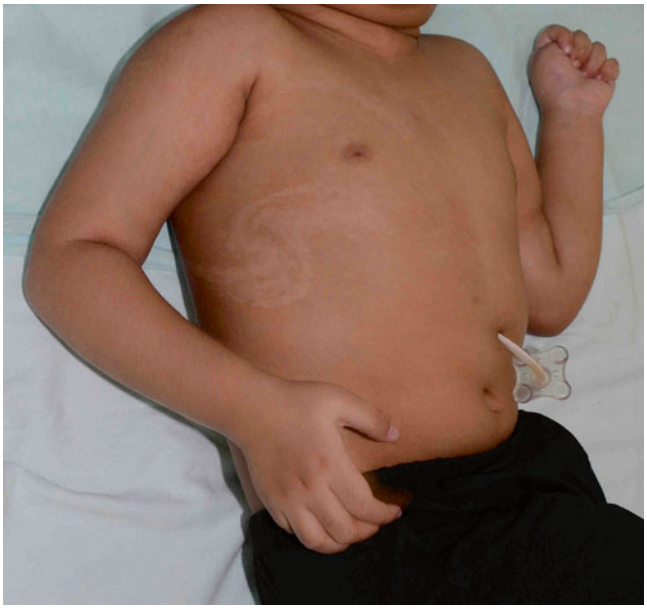

Fig. 3.18 Hypomelanosis of Ito. Hypopigmentation is distributed in swirls along the lines of Blaschko in this girl with neurological defect. The pigmentary disturbance is often noticed soon after birth and is non-progressive

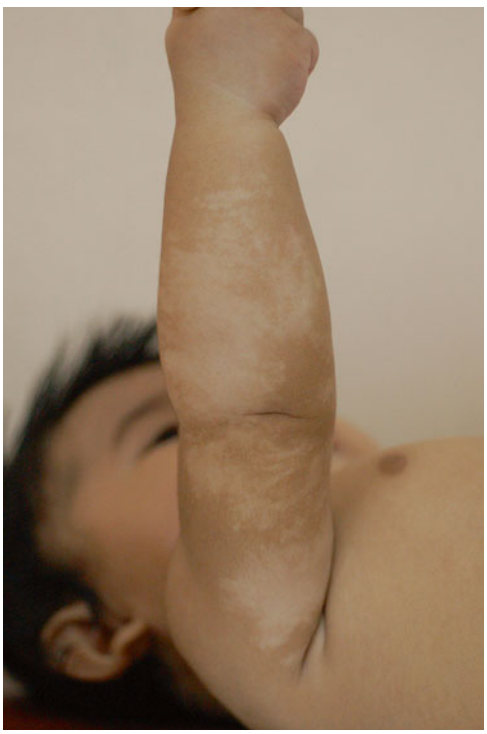

Fig. 3.19 Hypomelanosis of Ito. Hypopigmentation is distributed in linear fashion along the lines of Blaschko in this infant since birth

TSC is characterized by the formation of hamartomas in various organs, e.g., the brain, heart, lung, kidneys, and skin. It is an autosomal dominant disorder with almost complete

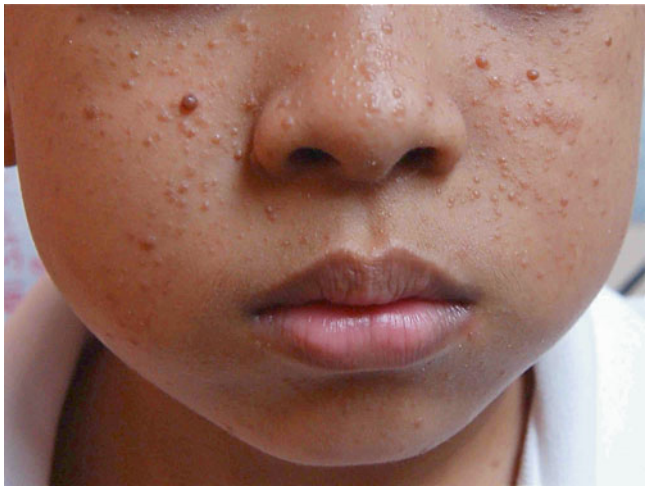

Fig. 3.20 Facial angiofibroma

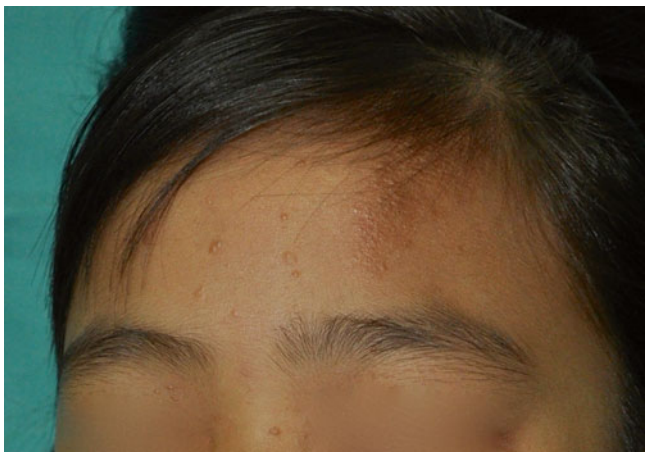

Fig. 3.21 Forehead fibrous plaque

penetrance but a wide range of clinical severity even among the siblings. Spontaneous mutation accounts for 66–86 % of cases [10, 11]. It has no predilection for gender.

The estimated prevalence of TSC is around one case for every 6,000–10,000 births [12]. A study in Taiwan revealed that the prevalence of TSC was estimated to be 1:95,136 and the prevalence for cases less than 6 years of age was 1:14,608 [13]. However, its true incidence is not known because of a number of undiagnosed cases consisting mostly of mildly affected or asymptomatic individuals.

TSC is caused by mutations of either the TSC1 gene on chromosome 9q34 encoding hamartin or the TSC2 gene on chromosome 16p13 encoding tuberin. Patients with TSC1 mutations generally have milder disease than patients with TSC2 mutation. The tuberous sclerosis gene products, hamartin and tuberin, form a tumor suppressor complex which drives Rheb (Ras homologue enriched in brain) into the inactive guanosine diphosphate-bound state.

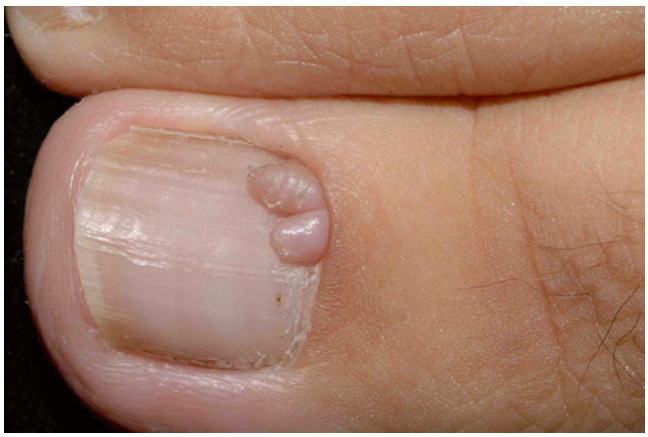

Fig. 3.22 Periungual fibroma

Fig. 3.23 Shagreen patch

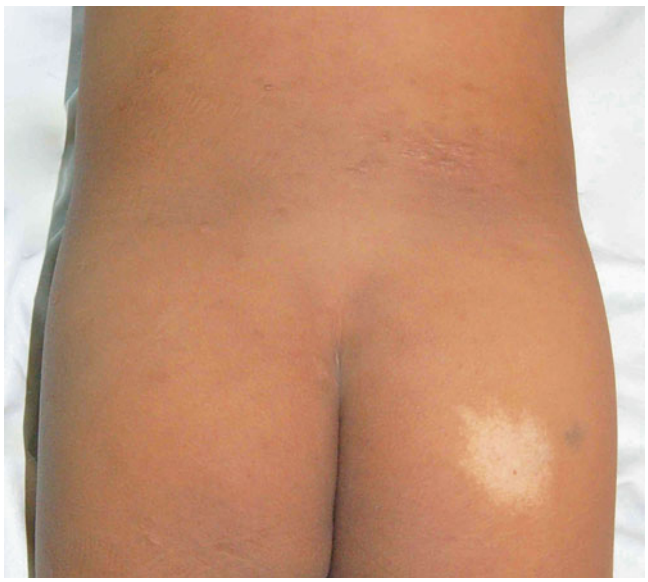

Fig. 3.24 Hypopigmented patch (polygonal)

Clinical Features

Among the diagnostic criteria for tuberous sclerosis complex, four major and one minor criteria are manifested on the skin.

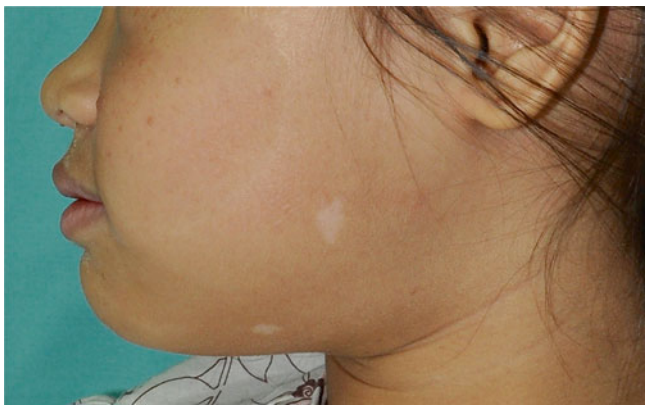

Fig. 3.25 Ash leaf macule

Table 3.4 Skin findings of tuberous sclerosis complex

	Age of onset	Prevalence
Hypomelanotic macules	Usually at birth or infancy	97.2 %
Facial angiofibroma	2–5 year-old	74.5 %
Shagreen patch	Rarely at birth. Increase its size with age	48.1 %
Forehead fibrous plaque	Can be seen at birth or early infancy	18.9 %
Periungual fibroma	Present at puberty or soon after	15.1 %

1. Facial angiofibroma (Fig. 3.20) and forehead plaque (Fig. 3.21)
2. Nontraumatic ungual or periungual fibroma (Fig. 3.22)
3. Shagreen patch (Fig. 3.23)
4. Hypomelanotic macules in polygonal or ash leaf shape (3 or more) (Figs. 3.24 and 3.25)
5. Hypomelanotic lesions in "Confetti" pattern (minor)

The skin findings have important diagnostic value because they are common and readily identifiable by routine physical examination. They **may be the only clues that the dermatologist has to the diagnosis of TSC**. The prevalence and age of onset of these findings are listed in Table 3.4 [14].

Hypopigmented Skin Lesions in TSC

Hypopigmented macules or patches are the earliest sign of TSC and are present in up to 90 % of patients.

Morphology: The macules and patches in TSC are hypopigmented, well defined with non-scaly surface. Its shapes vary from polygonal to ash leaf or arranged in confetti pattern.

Distribution and pattern: These lesions are found mainly over the body and extremities.

Clinical course: Hypopigmented skin lesions in TSC are usually detected at birth and their size increases according to body size.

Differential Diagnosis

A single hypopigmented macule is common and has been described in 0.2–0.3 % of all neonates [15]. They need to be differentiated from those listed in group A(1).

Other major findings as stated below are not readily available by physical examination and often need radiological imaging for detection and confirmation.

- Cortical tuber, subependymal nodule, subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

The classic diagnostic triad of seizures, mental retardation, and facial angiofibromas is evident in only 29 % of cases; 6 % of TSC patients have none of these three findings [16].

Management

Management is multidisciplinary and individualized based on their severity and organs involved. As TSC has variable penetrance and its clinical signs are progressive, regular follow-up is mandatory as certain signs appear later in life. Camouflage and photoprotection is beneficial for the hypopigmented lesions. Carbon dioxide, pulsed dye laser, and topical sirolimus/rapamycin [17] are helpful for facial angiofibromas, but slowly recur once the treatment stopped.

Genetic counseling is helpful, but its benefit is often limited by its wide variation in genetic expression and the high frequency of spontaneous gene mutation in TSC. A careful family history, skin examination, and relevant imaging of other family members are recommended.

Group A-2: Early-Onset Depigmentary Disorder

Piebaldism

Introduction

Piebaldism is a rare autosomal dominant disorder characterized by congenital poliosis and leukoderma. It results from mutations of the c-kit gene on chromosome 4q11–12 [18].

A mutation in the c-kit proto-oncogene results in abnormal tyrosine kinase transmembrane cellular receptors and causes abnormal melanocyte embryogenesis with defective melanoblast proliferation, migration, and distribution. There is absence of melanocytes and melanin production within the depigmented lesion.

Clinical Features

Morphology

The areas of depigmented white patches are irregular, well-demarcated, and milky white in color. There is presence of islands of normal pigmented and hyperpigmented macules within these depigmented patches. This is typical and helpful in the clinical diagnosis.

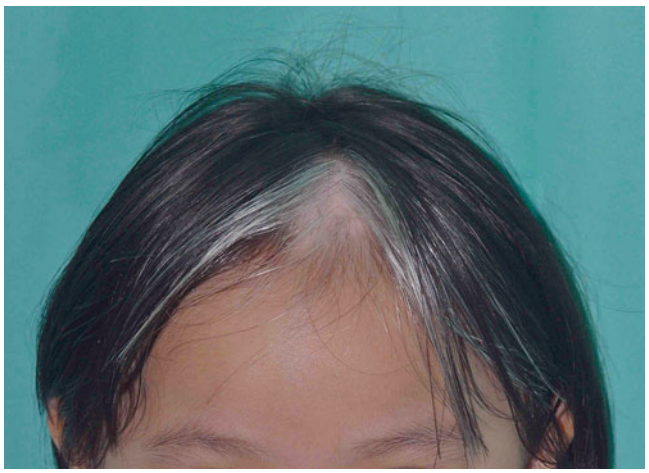

Fig. 3.26 Piebaldism. The *white* forelock is characteristic of piebaldism. *White* patches in piebaldism are present from birth and is a useful distinguishing feature from vitiligo. However, her eyebrows and eyelashes are not involved in this girl

Distribution and Pattern

Skin

The depigmented skin patches have a characteristic distribution pattern that favor the forehead, central chest and abdomen, upper arms, and lower legs. Posterior midline, hands, and feet are usually spared.

Hair

A white forelock which consists of a tuft of white hair over the midfrontal scalp is present in 80–90 % of patients with depigmentation of the underlying scalp (Fig. 3.26) [19]. However, its absence does not exclude the diagnosis. Poliosis of eyebrows and eyelashes may be seen.

Clinical Course

The lesions are present at birth but remain constant throughout life, although some variability in pigmentation may occur with sun exposure.

Extracutaneous Findings

Except for the depigmented skin lesions, most patients with piebaldism are otherwise healthy. There are rare reports of piebaldism associated with neurofibromatosis type 1 [20, 21], Hirschsprung disease, and deafness.

Differential Diagnosis (Table 3.5)

1. **Vitiligo**

   Morphologically, vitiligo and piebaldism are similar with well-demarcated depigmented patches. But the presence of stable depigmented patches since birth, family history, the

Table 3.5 Clinical features of piebaldism, early onset vitiligo and Waardenburg's syndrome

	Piebaldism	Vitiligo	Waardenburg's syndrome
Morphology	Depigmentation Well defined With areas of normal or hyperpigmentation	Depigmentation Well defined	Depigmentation
Distribution			
Skin	Central forehead mid arms/legs Sparing hands/feet	Periorificial	Face, neck, body and dorsal limbs
Hair/eyebrow	Poliosis	Poliosis	Poliosis
Mucosal	Spared	Present	Present
Clinical course	Present at birth Non-progressive	At any age, but rarely at birth Usually progressive	Present at birth Non-progressive
Extracutaneous	Usually isolated	Autoimmune conditions e.g., thyroiditis	Heterochromia irides Deafness
Histology	Absence of melanocyte	Absence of melanocytes	Absence of melanocytes

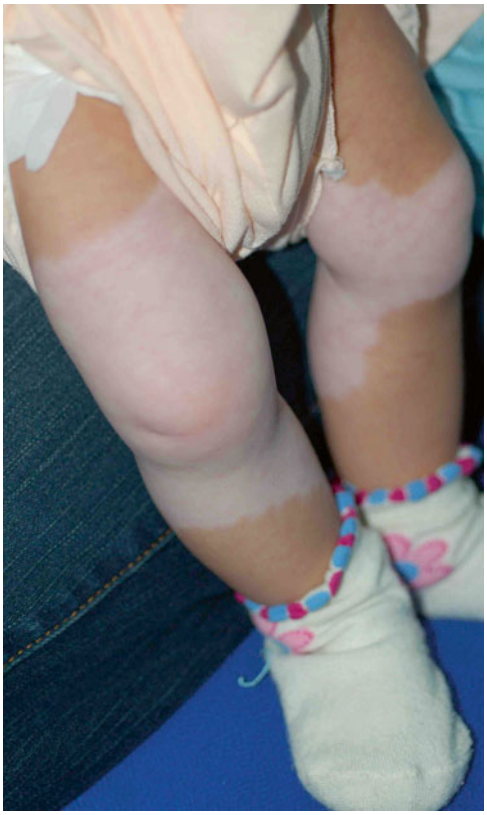

Fig. 3.27 Waardenburg syndrome. The depigmented skin patches have a characteristic distribution pattern that involved mid portion of both lower legs since birth. Both feet are spared. He had a white forelock, lateral displacement of inner canthi (inner canthal distance divided by the interpupillary distance is >0.6) and hearing impairment

characteristic distribution pattern, and islands of normal or hyperpigmented macules within the areas of depigmented patches allow the differentiation of piebaldism from vitiligo.

2. **Waardenburg syndrome (WS)**
   WS needs to be considered for all children with piebaldism. Ocular and hearing assessment is mandatory. Piebaldism (Fig. 3.27), facial dysmorphism, heterochromia of the irides, and sensorineural deafness are the main features of Waardenburg syndrome. WS has been divided into four variants (WS1–WS4). Both WS1 and WS2 are transmitted as autosomal dominant conditions with interfamilial and intrafamilial variability. Two far rarer variants WS 3 and 4 include features of WS in association with severe contractures and Hirschsprung disease, respectively [22, 23].

Treatment of Piebaldism

Most treatments (e.g., topical calcineurin inhibitor, topical corticosteroid, and phototherapy) are not efficacious. Photoprotection of the depigmented areas is important to protect against sunburn and skin cancer. Cosmetic camouflage can be recommended and helpful. Autologous cultured melanocyte grafts may be worthwhile in selected patients, but this often requires multiple sessions.

Group B: Early-Onset Generalized Diffuse Hypopigmentation

Generalized diffuse hypopigmentation of early onset describes those extensive hypopigmentary disorders that occur from birth up to the first 2 years of life. As neonates often have a lighter skin at birth, some of these congenital hypopigmented lesions can easily **go unnoticed** until later in infancy. In addition to age of onset, they can be further subcategorized into with or without ocular involvement (Table 3.1).

Diffuse and early-onset hypopigmentation in children often has an underlying genetic cause. Hence, a detailed family tree is mandatory. In all of the disorders outlined in group B, the epidermis generally contains normal numbers of melanocytes and histological findings under light microscope are often not helpful in differentiating these conditions. The pathophysiological defect of hypopigmentation lies in either melanin biosynthesis or melanosome formation and trafficking.

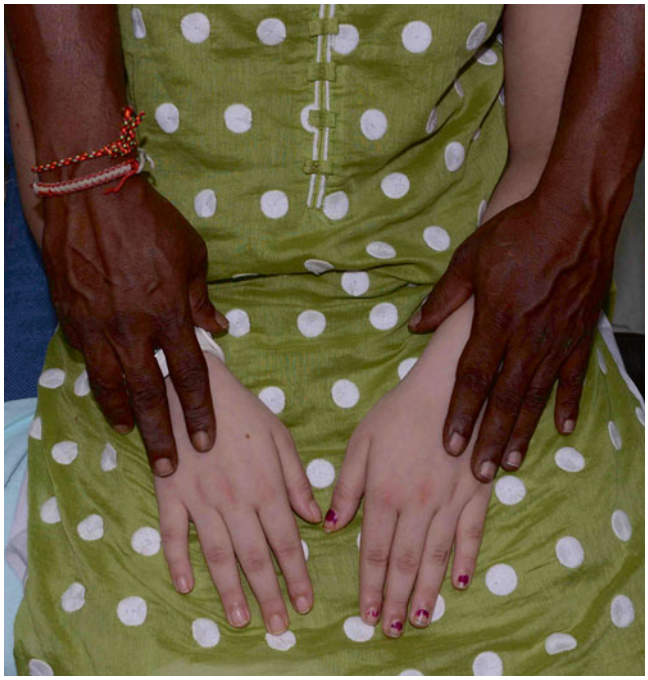

Fig. 3.28 Albinism. Hands of the patient and her father

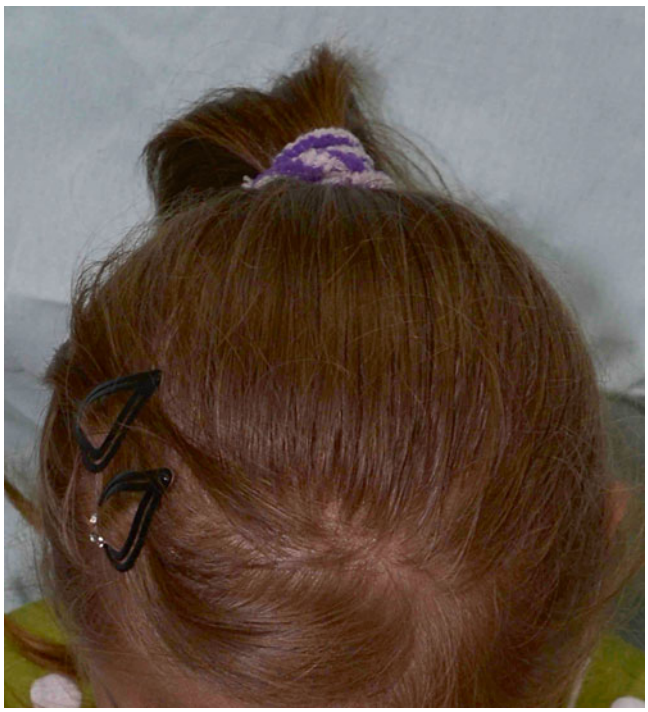

Fig. 3.29 Albinism

Group B-1: Early-Onset Generalized Diffuse Hypopigmentation with Skin, Hair, and Eyes Involvement

Oculocutaneous Albinism

General features of albinism are as below

(A) It is a heterogeneous group of pigmentary disorder manifested by generalized hypopigmentation or depigmentation of the skin, eyes, and hair that has onset at birth (Figs. 3.28, 3.29, and 3.30)

In oculocutaneous albinism (OCA) type 1A, there is permanent and complete absence of pigment from birth. In OCA types 1B, 2, 3, and 4, however, pigment production may increase over time.

(B) Historically, OCA is divided only into two clinical types: tyrosinase positive or negative. Advances in molecular genetics and better understanding of genotype–phenotype correlation have given rise to a more accurate classification of Albinism into seven groups.

(C) All of them are autosomal recessive. Both sexes are equally involved.

(D) In OCA, epidermal melanocytes are present in normal amount and distribution but do not synthesize adequate melanin due to tyrosinase defects or melanosomal dysfunction.

(E) Overall, an estimated 1 in 20,000 people worldwide are born with oculocutaneous albinism. The condition affects people in many ethnic groups and geographical regions. Types 1 and 2 are the most common forms of this condition; types 3 and 4 are less common. However, particular types of albinism are more common in different parts of the world. Studies suggest that type 4 occurs more frequently in the Japanese and Korean populations than in people from other parts of the world [23]. Hermansky–Pudlak syndrome is the most common type of albinism in Puerto Rico, with a frequency of 1 case per 2,700 population. This disorder is very rare in other parts of the world. The first case of adult Hermansky–Pudlak was documented in Malaysia in 2012 [24].

(F) Common to all types of OCA, there is reduced visual acuity and ocular nystagmus and these distinguish OCA from other forms of congenital diffuse hypopigmentation. The ocular abnormalities are due to misrouting of the optic nerve and this may result from deficiency of tyrosinase.

(G) In routine clinical practice, babies with early diffuse hypopigmentation that involve skin, hair, and eyes should undergo a systemic evaluation to exclude other

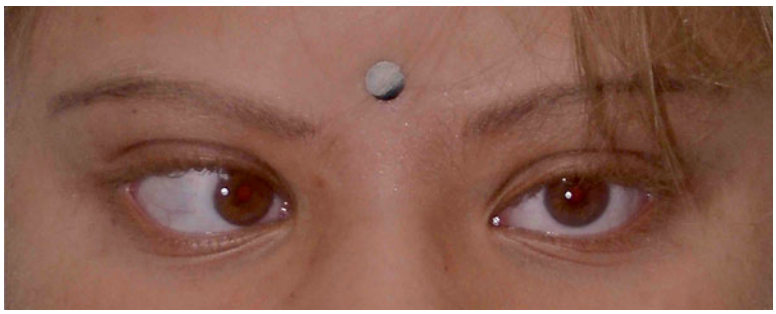

Fig. 3.30 Albinism and hypochromic iris

rarer disorders. For example, the presence of bleeding diatheses may be a sign of Hermansky–Pudlak syndrome and primary immune deficiency with recurrent infections points to Chediak–Higashi syndrome. If mental retardation with neurological regression is identified, blood and urine investigation is indicated to rule out phenylketonuria. Other inborn errors of metabolism, i.e., histidinemia and homocystinuria, can cause generalized diffuse hypopigmentation too (Table 3.6)

(H) In terms of treatment, the aggressive sun protection to prevent actinic damage and early development of skin cancer is needed. Regular eye assessment is essential for their eye problems. Correction of refractive errors with spectacles or contact lenses improves visual acuity. Dark glasses may alleviate photophobia.

(I) In terms of its psychosocial impact , albinism often has social ramifications because patients may get stigmatized as a result of the difference in appearance from their families, peers, and other members of their ethnic group. This is true especially among skin of color.

Group B-2: Early-Onset Generalized Diffuse Hypopigmentation with Skin and Hair Involvement

For children with early-onset generalized diffuse hypopigmentation, full eye assessment and follow-up is essential in the diagnostic process. This is because some genetic disorders, e.g., Griscelli, Elejalde, and Menkes syndromes (Table 3.7), result in pigmentary dilution of the skin and hair, but spare the eyes. These patients should also be screened for neurological, immunological, and other systemic abnormalities (Table 3.8). Other conditions that need to be considered are ectrodactyly–ectodermal dysplasia–cleft lip/palate (EEC) syndrome and selenium deficiency among patient on long-term total parenteral nutrition [25].

Group C+D: Late-Onset Localized and Generalized Hypopigmentation

Late-onset localized and generalized hypopigmentary disorders listed in Table 3.1 are discussed together because many of them, e.g., post-inflammatory hypopigmentation, mycosis fungoides, and pityriasis alba, can assume either of these patterns.

Pityriasis Alba

Introduction

This is a benign childhood inflammatory skin disease that was first described by Fox in 1923 [37]. It is seen most often in children and adolescents and more obvious in skin of color. Both genders are equally affected and it is more common among children with atopic eczema. It is regarded as a minor feature of atopic dermatitis. One-quarter of pediatric and adolescent atopic eczema patients in Singapore have been reported to have pityriasis alba [38]. The underlying cause of PA remains unclear. It is probably a chronic dermatitis that results primarily from inflammation of the epidermis and superficial dermis that can interfere with the normal melanosome transfer from melanocytes to keratinocytes .

Clinical Features

Morphology

Pityriasis alba is characterized by multiple ill-defined hypopigmented macules or patches. Its surface is minimally scaly with its edges often blending imperceptibly into the normal skin.

Distribution and Pattern

Pityriasis alba is commonly seen on both sides of the face, particularly the cheeks (Fig. 3.31). Less often, lesions are found on the upper extremities and shoulders and rarely elsewhere.

Clinical Course

The hypopigmented macules/patches may persist for months or years, but often resolves spontaneously at puberty. The

Table 3.6 Classification of disorder with cutaneous and ocular albinism

Disorder	Genetics	Pathogenesis	Clinical features
OCA Type 1 A (Tyrosinase negative)	Autosomal recessive TYR gene on chromosome 11q14–q21	Mutation in tyrosinase (TYR) gene with absent of tyrosinase activity As a result, melanosomes contain no melanin	1. **Skin and hair and eyes** (a) Skin: white to pale pink (b) Hair: white (c) Eye: gray translucent iris with visual impairment and nystagmus No retinal pigment 2. **Onset and progression** (a) Onset at birth (b) No improvement with age. However, the hair may become yellowish later in later life
OCA type 1B (Tyrosinase positive)	Autosomal recessive TYR gene on chromosome 11q14–q21	Mutation in Tyrosinase (TYR) gene with variable reduction in tyrosinase activity Tyrosinase activity is temperature-sensitive	1. **Skin and hair and eyes** (a) Skin: white to light pigmented (b) Hair: white to light yellow (c) Eye: gray translucent iris with visual impairment 2. **Onset and progression** [26] (a) Onset at birth and develop some pigmentations with age (b) Pigmented nevi and freckles are present
OCA type 2 (Tyrosinase positive)	Autosomal recessive P gene on chromosome 15q11.2–q12 [27]	Mutation in P gene that involving in tyrosinase processing and transport [28]	1. **Skin, hair and eyes** (a) Skin: creamy white to light brown (b) Hair: light yellow to light brown (c) Eye: blue, tan, hazel irides with visual impairment, nystagmus and minimal retinal pigment 2. **Onset and progression** (a) Onset at birth and darken with age (b) Freckles and pigmented nevus are seen
OCA Type 3 (Rufous)	Autosomal recessive TYRP1 gene on chromosome 9q23 [29]	Mutation in TYRP1 gene that encodes dihydroxyindole carboxylic acid oxidase [30]	1. **Skin, hair, eyes** (a) Skin: light brown to red bronze (b) Hair: light brown to red brown (c) Eyes: light brown with nystagmus 2. **Onset and progression** (a) Onset at birth and may darken with age (b) No freckles and nevus
OCA type 4	Autosomal recessive MATP gene on chromosome 5p13.3	Mutation in MATP gene that encodes melanosomal protein [31]	1. **Skin, hair and eyes** (a) Skin: creamy white to brown (b) Hair: silvery white to light yellow at birth (c) Eye: light brown with nystagmus 2. **Onset and progression** (a) Onset at birth and may darken with age. Freckles seen
Hermansky–Pudlak syndrome	Autosomal recessive	HPS type 1–type 7 due to mutations of 7 different genes that encodes proteins involved in biogenesis of lysosome related proteins	1. **Skin, hair and eyes** (a) Skin: variable from creamy white to almost normal skin (b) Hair: creamy to red brown (c) Eye: blue to brown irides with visual impairment and nystagmus 2. **Onset and progression: onset at birth** 3. **Extracutaneous** Increased in bleeding tendency, pulmonary fibrosis, granulomatous colitis, renal failure and cardiomyopathy due to ceroid deposition
Chediak–Higashi syndrome	Autosomal recessive LYST gene on chromosome 1q42–1q43	Mutation of LYST gene that controls lysosome trafficking Giant lysosomes seen in many cells including neutrophils, monocytes, hepatocytes and melanocytes	1. **Skin, hair and eyes** (a) Skin: white skin (b) Hair: blond to silver (c) Eyes: blue to brown irides, strabismus and photophobia, minimal retinal pigment 2. **Onset and progression** (a) Onset at birth and may darken with age 3. **Extracutaneous** (a) Multiple infections and risk of lymphoma

course may be prolonged in atopic patients. The correct diagnosis of pityriasis alba is usually suggested by the age of the patient, fine scaling, hypopigmentation, and the distribution of lesions.

The differential diagnosis of localized pityriasis alba includes:

- Pityriasis versicolor
- Indeterminate or tuberculoid leprosy (Figs. 3.32 and 3.33)

Table 3.7 Group B-2: early onset generalized diffuse hypopigmentation of skin and hair only

Disorder	Genetic	Pathogenesis	Clinical features
Griscelli syndrome (GS)	Autosomal recessive 3 types identified (A) Type 1 GS [32] Mutation of MYO5A gene on chromosome 15q21 9 (B) GS type 2 [33] Mutation of RAB27A gene on chromosome 4 p13 (C) GS type 3 [34] Mutation of MLPH gene on chromosome 2q37	Defect in transport of lysosomal related organelle	Skin: diffuse hypopigmentation Hair: silvery gray hair, eyebrows, eyelashes Eye: not affected Extracutaneous features (a) GS type 1 : neurological defects (b) GS type 2: severe combined immunodeficiency with frequent infections (c) GS type 3: Isolated skin and hair Special finding: Histologically, the hair shafts reveal uneven clumps of melanin at the medulla
Elejalde syndrome	Autosomal recessive	Defect in transport of lysosomal related organelle	Skin: diffuse hypopigmentation Hair: silvery gray hair Eye: not affected Extracutaneous: Neurological deficit with severe hypotonia and seizure that onset from 1 month to 11 years of age [35]
Menkes syndrome	X-linked recessive Mutation of ATP7A gene that encodes copper transporting P-type ATPase	Malfunction of copper requiring enzymes Tyrosinase contribute to hypopigmentation Cross linkage for brittle hair Others for neurological and CT defects	Hair: sparse , short, lightly pigmented hair with a steel wool quality Skin: diffuse hypopigmentation with doughy laxity over the posterior neck, eyebrows and leg folds [36] Eye: not affected Extracutaneous: CNS deterioration with developmental regression Failure to thrive Special finding: Light microscopy showing pili torti with a flattened appearance with multiple twists of 180° around the long axis of the shaft

Table 3.8 Extracutaneous features of children with early onset generalized diffuse hypopigmentation

Extracutaneous features	Clinical diseases
Mental retardation and/or growth retardation	Angelman and Prader Willi syndrome Phenylketonuria Cross syndrome Griscelli syndrome Chediak–Higashi syndrome
Pulmonary fibrosis and granulomatous colitis	Hermansky–Pudlak
Bleeding diathesis	Hermansky–Pudlak
Primary immune deficiency with recurrent infections	Chediak Higashi/Griscelli
Eye abnormalities	Oculocutaneous albinism (all types) Cross syndrome
Total depigmentation with no freckle and pigmented nevus over age	OCA type 1A

It is a worldwide communicable disease mainly distributed in tropical and subtropical countries caused by *Mycobacterium leprae*. In tuberculoid leprosy, the initial lesion is often a sharply demarcated hypopigmented patch/plaque that is ovoid, circular, or serpiginous. As the disease progresses, lesions tend to affect the nerves and other skin appendages, i.e., sweat glands and hair follicles. The lesions may be somewhat elevated with a dry scaly center with hypo-anaesthesia, anhidrosis, and erythematous borders. Common lesion sites include the buttocks, face, and extensor surfaces of the limbs with predilection towards cooler zones, e.g., ears.

Histology reveals well-defined tuberculoid granulomas, with local destruction of nerves and appendages. Tuberculoid leprosy has good cell-mediated immunity and it represents the pauci bacillary forms of Hansen's disease. Hence, no acid fast bacilli are seen on histology with Fite stain and slit skin smear.

- Post-inflammatory hypopigmentation secondary to atopic eczema, seborrheic eczema (Fig. 3.34), psoriasis
- Early vitiligo

Treatment

Pityriasis alba is usually asymptomatic, but cosmetically noticeable especially among the Asian children. There is no universally effective treatment for pityriasis alba. Topical calcineurin inhibitor may be helpful in repigmentation of pityriasis alba [39, 40].Topical corticosteroid creams also have some influences on the disorder. Education about its benign and self-limiting clinical course is often needed to avoid unnecessary and potentially harmful treatment.

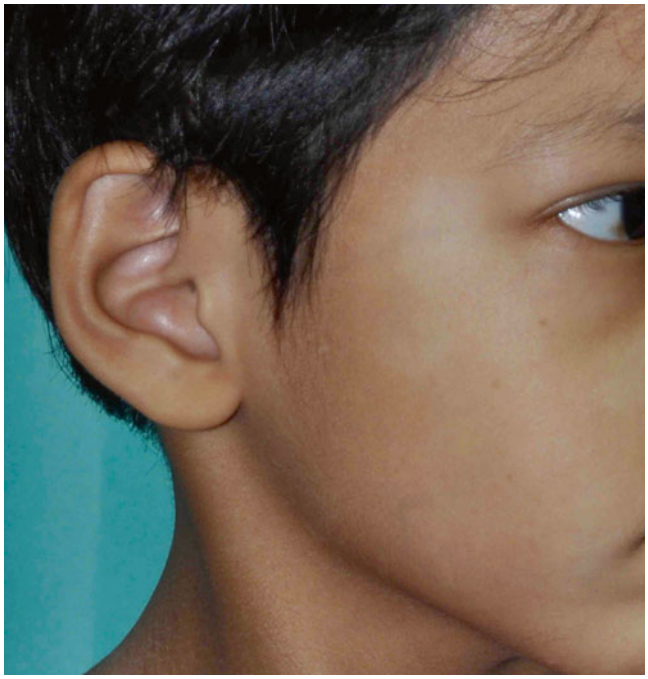

Fig. 3.31 Pityriasis alba

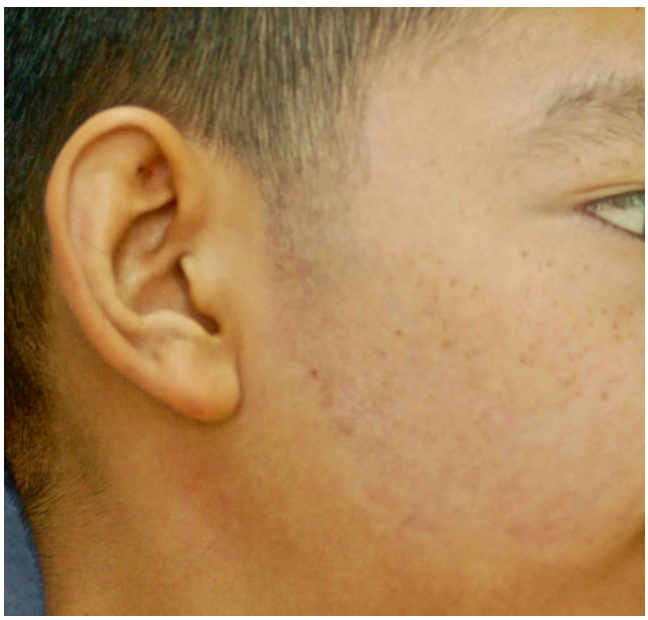

Fig. 3.32 Tuberculoid leprosy. Single well defined hypopigmented patches on his right cheek. There is loss of sensation, dryness, and anhidrosis over the lesion

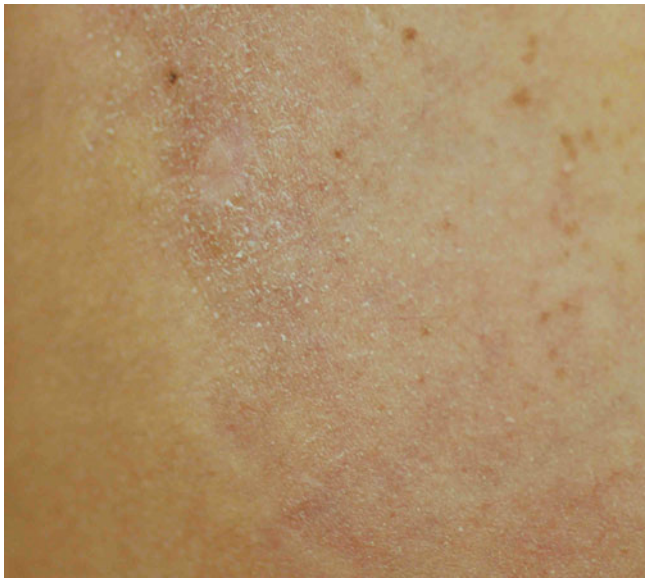

Fig. 3.33 Tuberculoid leprosy. Single well defined hypopigmented patches on his right cheek. There is loss of sensation, dryness, and anhidrosis over the lesion

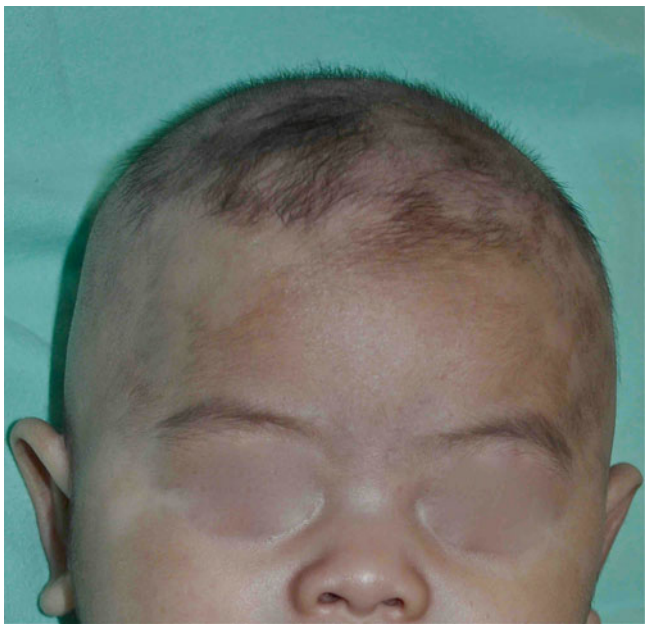

Fig. 3.34 Post-inflammatory hypopigmentation over his scalp and hair margin secondary to cradle cap

Pityriasis Versicolor

Introduction

Pityriasis versicolor (PV) is a common, superficial infection caused by the lipophilic yeast, Malassezia furfur. This condition is very common in the tropics with rates of up to 30–50 % in some tropical countries [41].

Clinical Features

Morphology

It appears as well-defined, round to oval macules that may coalesce to form large, geographic patches.

In dark skin types, lesions are typically off-white (Figs. 3.35 and 3.36).

In light skin types, lesions are typically darker from tan to brown (Fig. 3.36)

When scrapped lightly, they are very scaly which is a good diagnostic clue.

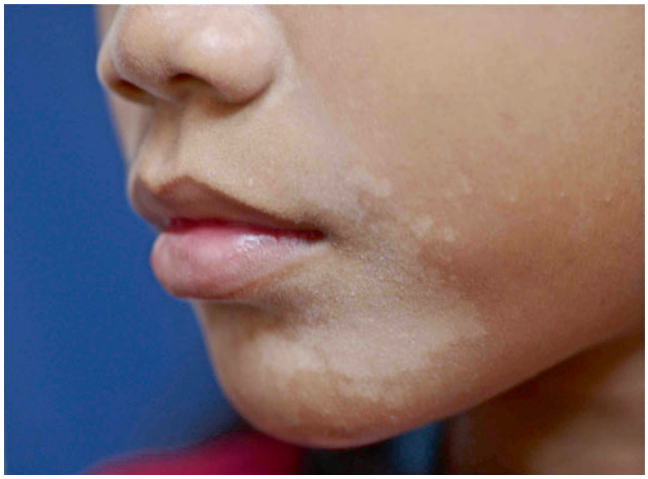

Fig. 3.35 Tinea versicolor. It presents as well-defined, hypo- or hyperpigmented (Fig. 3.36: left upper arm) macules with scaly surfaces. The macules may coalesce into patches over time

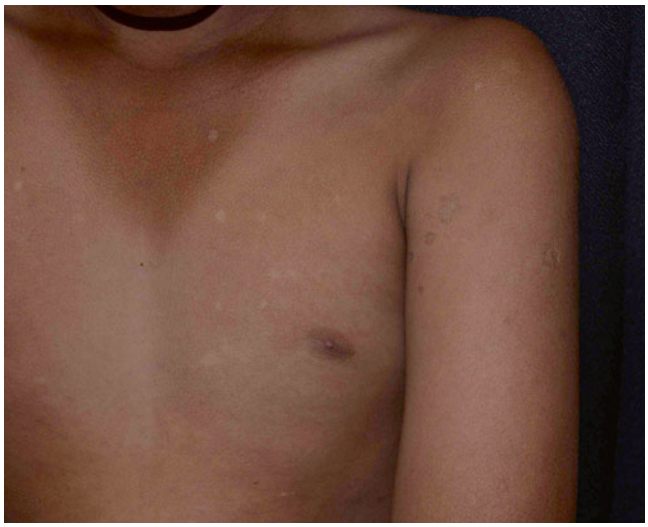

Fig. 3.36 Tinea versicolor. It presents as well-defined, hypo- or hyperpigmented (left upper arm) macules with scaly surfaces. The macules may coalesce into patches over time

Distribution

The upper chest is most commonly affected, but the lesions often spread to the upper arms and neck. Facial lesions are common in the tropics but rare in the temperate zones.

Diagnosis

Fungal scrapping and potassium hydroxide examination reveal hyphae and spores (so-called spaghetti and meatballs appearance) confirming the clinical diagnosis of PV.

Treatment

It includes topical or oral antifungal. However, the color may take months to recover. Avoidance of the usage of oral ketoconazole due to risk of liver damage has been recommended by the United States Food and Drug Administration.

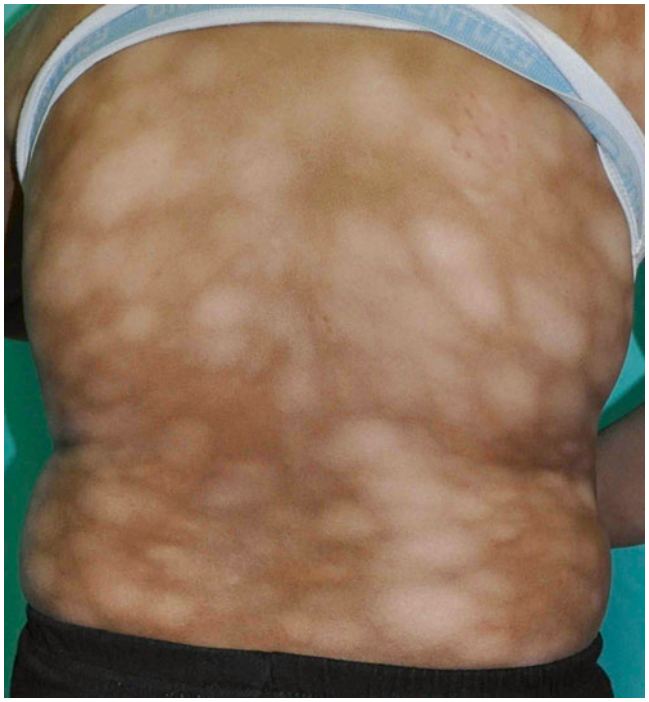

Fig. 3.37 Hypopigmented mycosis fungoides. This variant of mycosis fungoides affecting a 12-year-old Malay girl, who presents with multiple ill-defined hypopigmented patches involving the trunk, buttocks, and proximal extremities. These patches tend to be of varying sizes with slightly scaly and wrinkled surfaces (Fig. 3.39)

Mycosis Fungoides: Hypopigmented Variant

Introduction

Hypopigmented mycosis fungoides (HMF) is a unique variant of early-stage MF that was first reported by Ryan et al. in 1973 [42].

Hypopigmented mycosis fungoides affect primarily children and young adults with no sex predilection. This variant of mycosis fungoides is increasingly being described and recognized in our Asian population as well as other dark skin individuals.

Clinical Features

Morphology

HMF is characterized solely by hypopigmented patches or in combination with erythematous patches or plaques. The macules and patches enlarge gradually over months to years with ill-defined margins (Figs. 3.37, 3.38, and 3.39). Some lesions are atrophic, finely wrinkled, and slightly scaly.

Distribution

The hypomelanotic lesions are distributed asymmetrically in the bathing suit area—i.e., hips, buttocks, groin, lower trunk, axillae, and breasts.

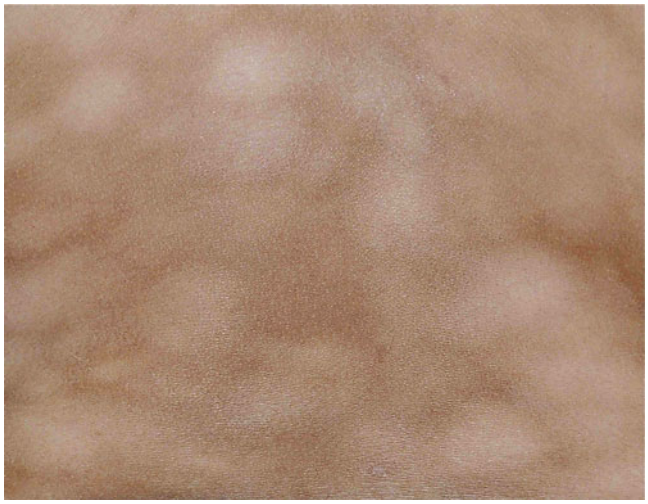

Fig. 3.38 Hypopigmented mycosis fungoides. This variant of mycosis fungoides affecting a 12-year-old Malay girl, who presents with multiple ill-defined hypopigmented patches involving the trunk, buttocks, and proximal extremities. These patches tend to be of varying sizes with slightly scaly and wrinkled surfaces (Fig. 3.39)

Fig. 3.39 Hypopigmented mycosis fungoides. This variant of mycosis fungoides affecting a 12-year-old Malay girl, who presents with multiple ill-defined hypopigmented patches involving the trunk, buttocks, and proximal extremities. These patches tend to be of varying sizes with slightly scaly and wrinkled surfaces

Clinical Course

The skin changes develop slowly, often over many years.

Differential Diagnosis

(A) **Pityriasis lichenoides chronica** (Figs. 3.40 and 3.41)
Pityriasis lichenoides chronica (PLC) is a papulosquamous disease of unknown etiology that most commonly affects children and young adults.

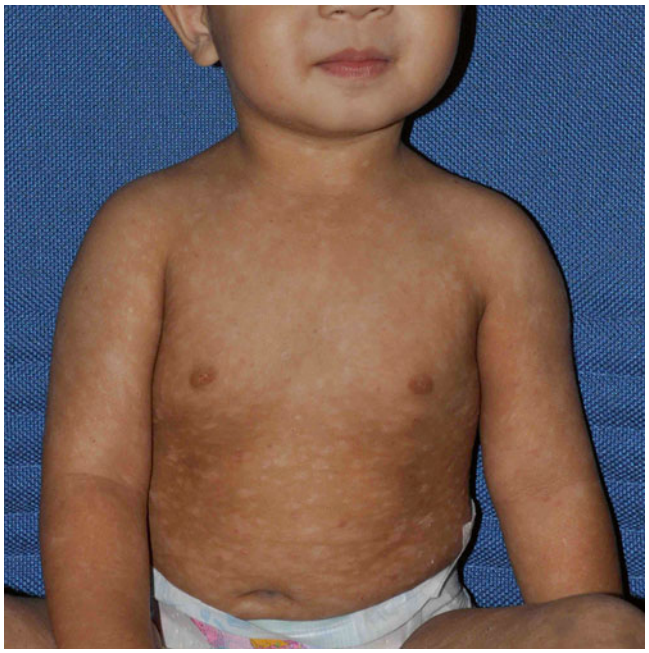

Fig. 3.40 Pityriasis lichenoides chronica. The primary lesion is brownish papule with scaly surface (Fig. 3.41). Resolving pityriasis lichenoides chronica often results in hypopigmentation in Asian skin which may persist for months

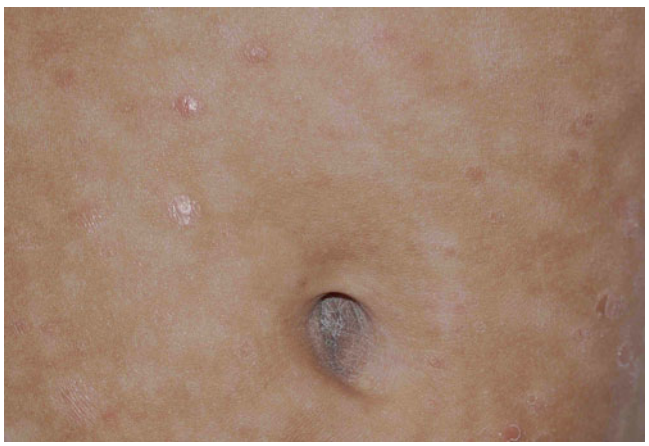

Fig. 3.41 Pityriasis lichenoides chronica. The primary lesion is brownish papule with scaly surface. Resolving pityriasis lichenoides chronica often results in hypopigmentation in Asian skin which may persist for months

Morphology

PLC presents as small discrete erythematous-to-reddish brown papules with a fine scaly surface which has been likened to frosted glass.

The eruption often is polymorphic, with lesions at different stages of evolution. Resolving PLC often results in hypopigmentation which may persist for months.

Distribution

Lesions are commonly found over the trunk, buttocks, and proximal extremities.

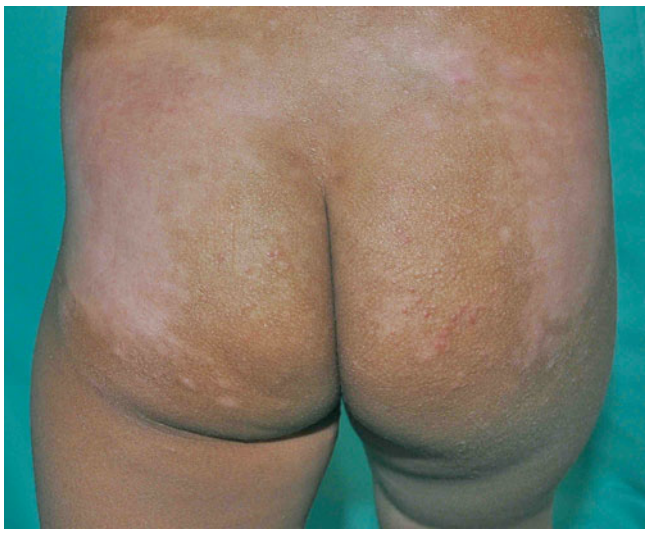

Fig. 3.42 Post inflammatory hypopigmentation secondary to toilet seat eczema

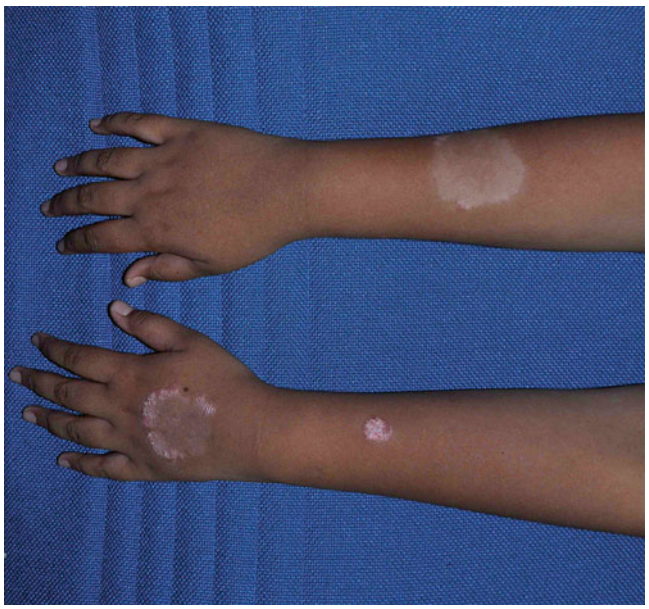

Fig. 3.43 Post inflammatory hypopigmentation secondary to psoriasis

Clinical Course

In some instances, it evolves out of PLEVA, but also occurs spontaneously.

Dark-skinned people may present with widespread macular hypopigmentation rather than the typical papular morphology [43]. This variant is most common in children. On biopsy, there is a modest lichenoid infiltrate with hyperkeratotic scale and parakeratosis noted.

(B) **Progressive macular hypomelanosis**
Progressive macular hypomelanosis (PMH), which is a common benign skin condition in Asians, usually starts on the back of the trunk in and around the midline, rarely extending to the buttocks, proximal limbs, and neck. PMH is characterized histologically by diminished pigment in the epidermis and a normal-looking dermis without epidermotropism.

(C) **Post-inflammatory hypopigmentation**
This refers to the partial loss of melanin in previously inflamed areas of skin, and is more obvious in darker skin type. Common primary events in children are seborrheic dermatitis, atopic eczema, irritant contact eczema (Fig. 3.42), psoriasis (Fig. 3.43), trauma, or drug eruptions.

Depending on the primary event, various size, shapes, patterns, and distribution of hypopigmented lesions may become visible. Most cases of post-inflammatory hypopigmentation revert to normal color after a variable period of months to years .Hence, no active treatment is necessary.

(D) **Pityriasis versicolor** (see section on P. 35-36)

(E) **Leprosy**

The diagnosis of mycosis fungoides is established by the clinical appearance of skin lesions and histopathologically. Early in the course of the disease, skin lesions may be nonspecific, with a non-diagnostic biopsy result, and so confusion with benign conditions is common. A skin biopsy obtained from untreated and clinically suspicious areas is usually required to confirm the diagnosis, but this may have to be repeated before the diagnosis can be made. Skin biopsy shows basal alignment and epidermal infiltrations of atypical lymphocytes (Pautrier's abscesses) with minimal spongiosis, hyperconvoluted dermal and epidermal lymphocytes, and "grandiosity" sign (size of lymphocytes becoming larger as they migrate towards the granular layer of the epidermis).

For borderline cases, regular and long-term follow-up is mandatory.

Treatment

Overall survival rate and disease-specific survival rates at 5, 10, and 20 years were 98 % in hypopigmented MF and risk of disease progression at 5,10, and 20 years was 9 % in hypopigmented MF in an analysis published by Agar et al. [44].

Vitiligo

Introduction

Vitiligo is an acquired disorder in which there is an absence of functional melanocytes and complete loss of pigment in the involved areas. It affects approximately 0.5–2 % of the general population worldwide.

About half the patients present before age of 20 years and nearly 70–80 % before the age of 30 years. But it may appear any time from shortly after birth to adulthood. No sex predisposition is noted.

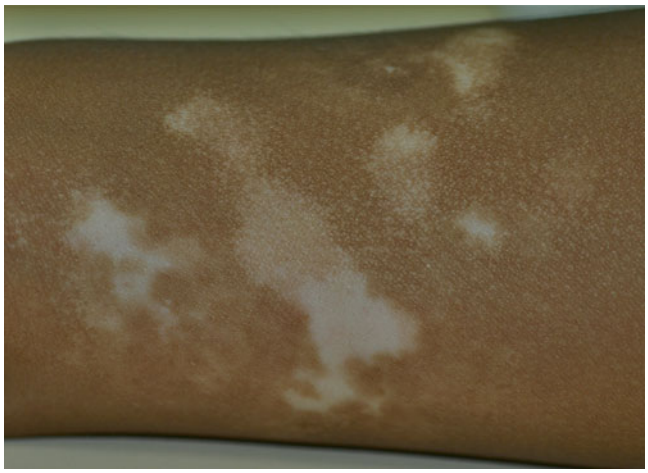

Fig. 3.44 Trichrome vitiligo. It has been described where there are white, intermediate, and normal hues from the center to the periphery of the lesion

Etiology

Vitiligo is a multifactorial disorder related to both genetic and nongenetic factors. It is considered an autoimmune disease, but the precise etiology is not clearly understood. Besides autoimmune destruction of melanocytes, other proposed mechanisms include self-destruction because of aberrant tetrahydrobiopterin synthesis, defective free radical defenses, and destruction of melanocytes by neurochemical substances. It is likely that destruction of melanocytes may be the result of a combination of several different mechanisms.

Clinical Features

Morphology

Vitiligo presents as well-demarcated, uniformly chalk-white depigmented macules and patches. The macules are oval and/or round in shape, often with scalloped margins.

In vitiligo skin there is no surface change and usually no redness. Occasionally, inflammation and hyperpigmentation are seen at the advancing edge of a vitiligo macule. Other morphological variants include guttate (Fig. 3.44), trichrome vitiligo (Fig. 3.45), and quadri-chrome vitiligo.

Distribution and Pattern

Vitiligo may occur anywhere on the body, but there are characteristic patterns of involvement. It is commonly found over sites that are normally hyperpigmented and areas subjected to repeated trauma, such as face, dorsal aspects of hands and feet, bony prominences, and anogenital regions or surgical scars (Fig. 3.46).

The following clinical classification is useful

- Localized—focal/mucosal/segmental (Figs. 3.47 and 3.48)
- Generalized—acrofacial/vulgaris/universalis (Fig. 3.49)

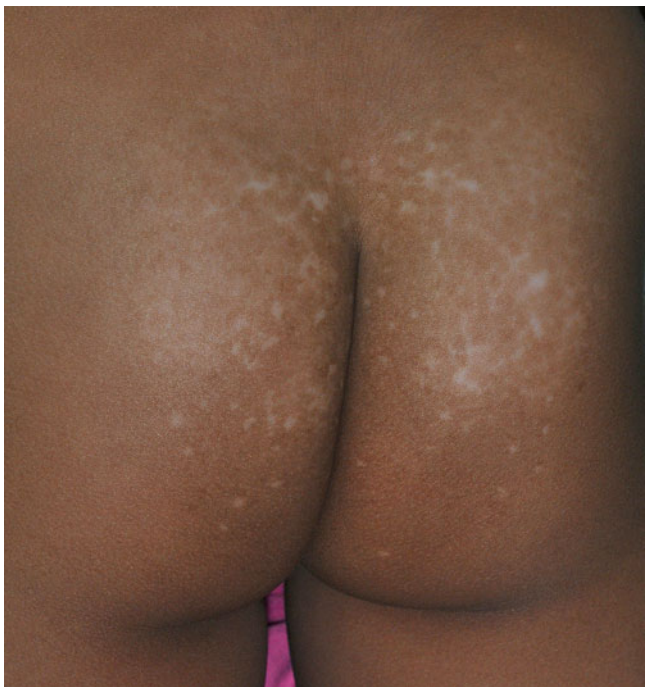

Fig. 3.45 Guttate or punctate vitiligo

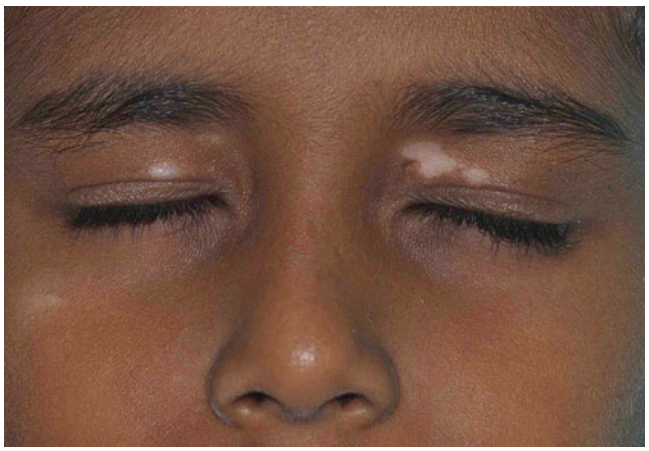

Fig. 3.46 Peri-orbital vitiligo. This child has developed focal depigmentation around the eyes

Extracutaneous

Most vitiligo patients are generally healthy.

But many autoimmune diseases are associated with vitiligo: either patients with vitiligo are more likely to be affected, or patients with the disease are more likely to have vitiligo.

The strongest association is with thyroid dysfunction, either hyper- or hypothyroidism. Others include pernicious anemia, Addisonian disease, morphea, uveitis, and diabetes mellitus.

A single-center study of 213 patients aged 17 years or younger with segmental or nonsegmental vitiligo found that nonsegmental vitiligo was more strongly linked than segmental

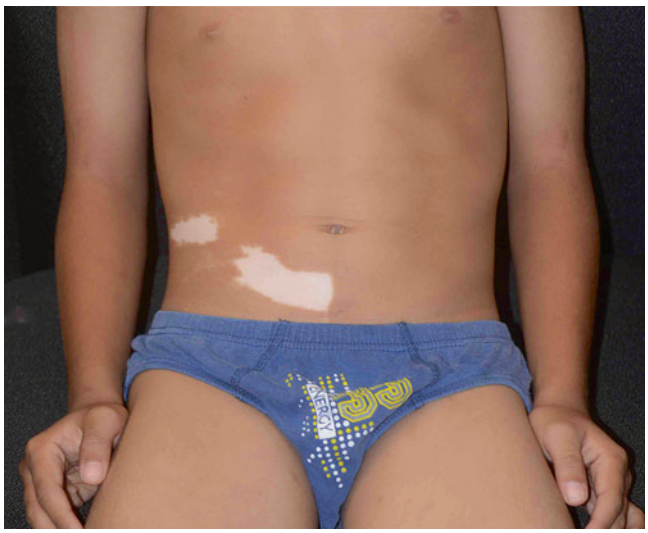

Fig. 3.47 Segmental vitiligo. This child has unilateral segmental vitiligo of the right lower abdomen

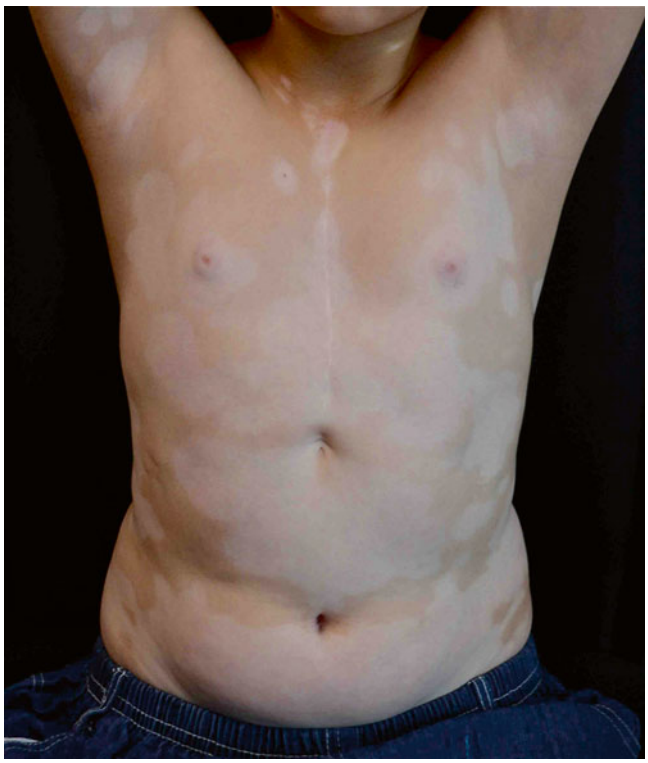

Fig. 3.48 Generalized vitiligo. This young Chinese patient has extensive vitiligo on his trunk and extremities symmetrically

vitiligo to markers of autoimmunity or inflammation such as halo nevi and thyroid antibodies; patients with nonsegmental vitiligo were also more likely to have a family history of vitiligo or autoimmunity [45].

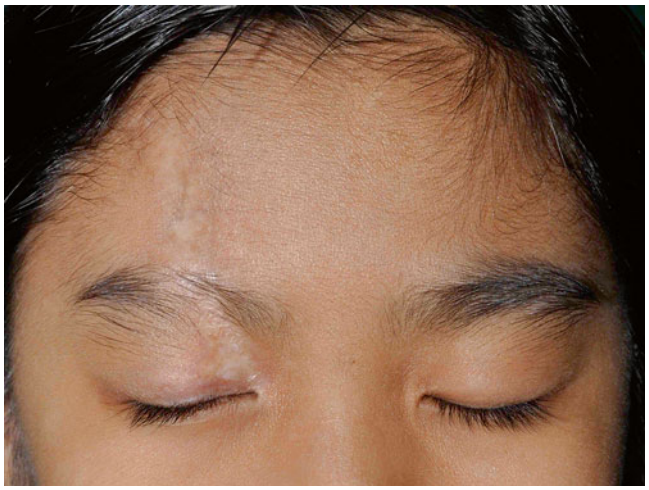

Fig. 3.49 En coup de sabre. A narrow, depressed, linear sclerotic band on the forehead of this young girl

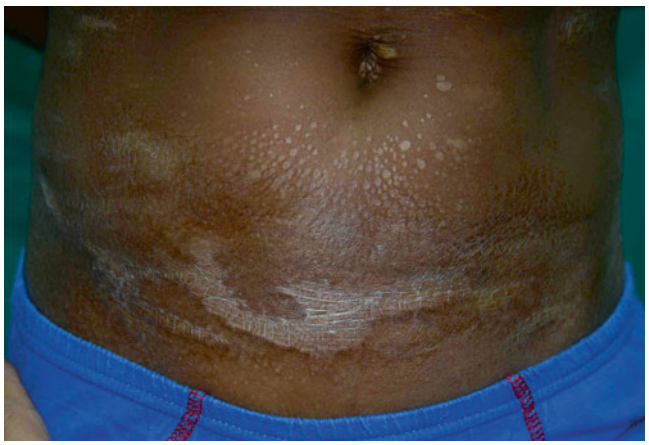

Fig. 3.50 Generalized morphea. Multiple hypopigmented sclerotic plaques were noted over his abdomen. Destruction of the underlying appendages is permanent in morphea and the overlying skin appeared smooth and shiny

Clinical Course

The onset of vitiligo is insidious and its clinical course is unpredictable. A study from South Korea reported progressive disease in more than 90 % of a series of 318 patients with vitiligo. It suggested that progression rather than spontaneous resolution is the norm [46].

Differential Diagnosis

1. **Morphea**

   Hypopigmentation is not uncommonly seen in lesions of morphea and systemic sclerosis. Morphea is characterized by early violaceous plaques that later progress to ivory white sclerotic areas with wrinkled surface, which may be solitary, linear (Fig. 3.49), or generalized (Fig. 3.50).

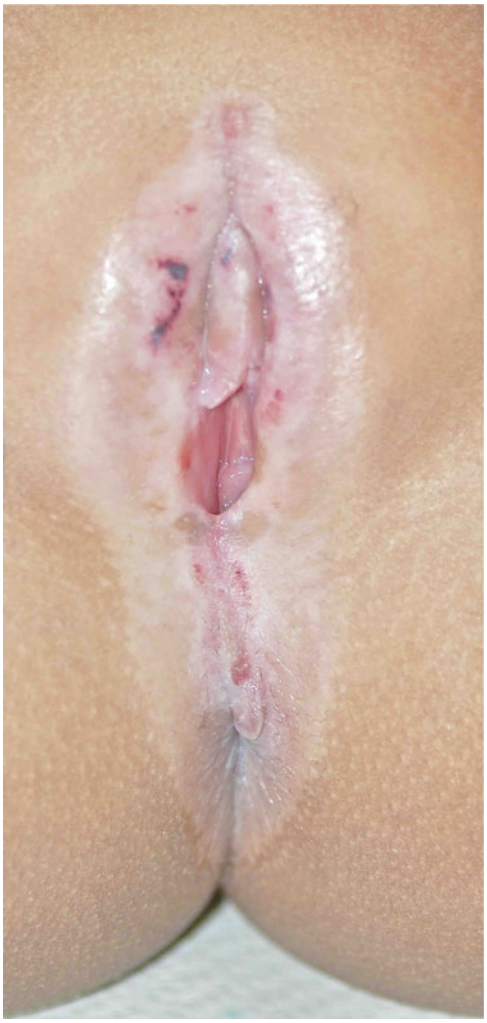

Fig. 3.51 Lichen sclerosus et atrophicus

Over a period of months to years, the surface becomes smooth and shiny, with loss of hair follicles and sweat glands. Hypo- or hyperpigmentation often ensues as lesions evolve. Skin surface changes and dermal induration are absent in vitiligo.

2. **Lichen sclerosus et atrophicus** (Fig. 3.51)
Lichen sclerosus is a pruritic chronic inflammatory dermatosis primarily of the superficial dermis that affects women more often than men. It presents as hypopigmented to depigmented porcelain white patches or plaques with a sharply demarcated border. Commonest site is anogenital area. It has a shiny wrinkled surface and may develop hemorrhage and erosions with trauma.

Other differential diagnoses include halo nevus (Fig. 3.52), pityriasis alba, post-inflammatory hypopigmentation or leukoderma, tinea versicolor, nevus depigmentosus, and piebaldism.

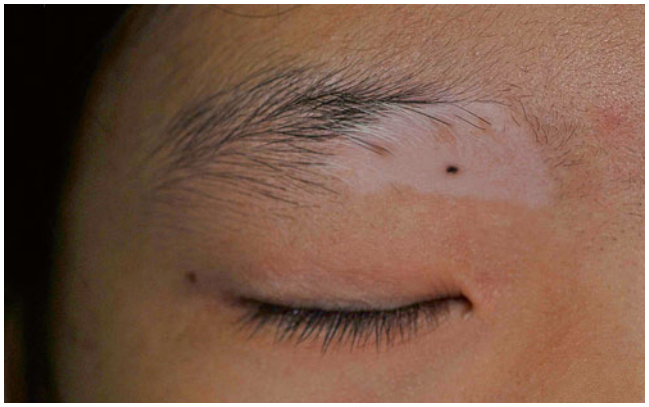

Fig. 3.52 Halo nevus with poliosis

Treatment

Treatment modalities for childhood vitiligo include topical corticosteroids, calcineurin inhibitors (Figs. 3.53 and 3.54), phototherapy, autologous transplantation for stable vitiligo, cosmetic camouflage, and sun protection [47]. Patients who have widespread disease with a few areas of normally pigmented skin can be treated with depigmenting agents.

A few issues that need to be addressed during patient counseling include:

(a) Understand that vitiligo is chronic and highly unpredictable
(b) Avoid trauma to minimize koebnerization
(c) Significant psychosocial impact especially among skin of color
(d) Partial repigmentation may not be cosmetically satisfactory

Group E: Localized and Circumscribed Hyperpigmented Disorders (Single to a Few Lesions)

Based on the level of melanin excess, they can be further divided into two groups:

Group E-1: **brown black** and Group E-2: **blue gray**

Color variation of melanin depends on its location in the skin. Due to Tyndall effect, melanin appears black in the epidermis, at the dermo-epidermal junction it appears brown, in the papillary dermis it appears gray, and in the reticular dermis it appears blue [48]. An excess of melanin in both the epidermis and the dermis together may also occur in some conditions.

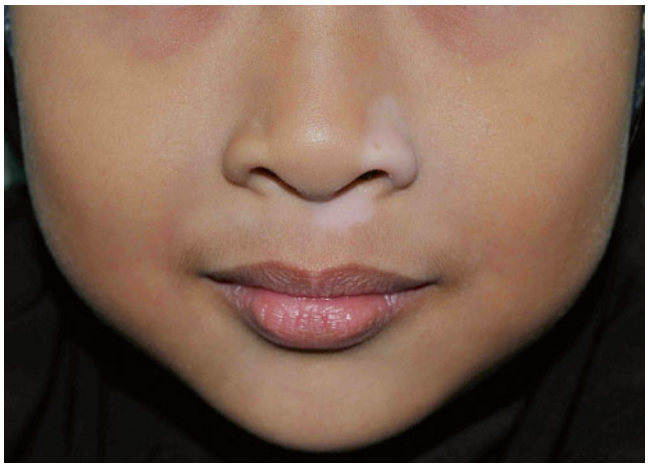

Fig. 3.53 Facial vitiligo prior to therapy

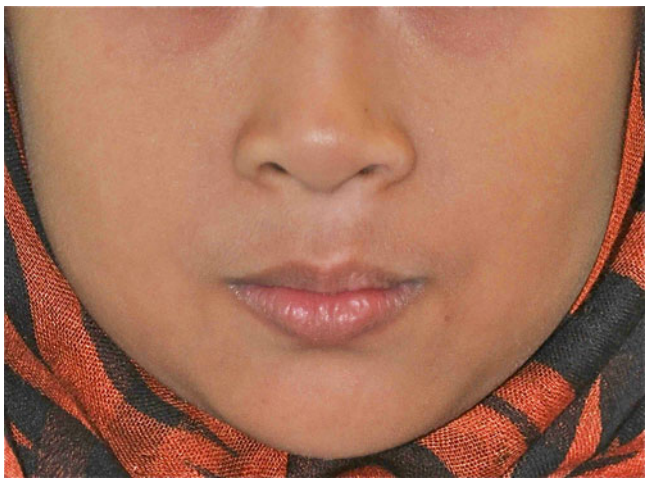

Fig. 3.54 Facial vitiligo. The same patient featured in Fig. 3.53 now showing excellent response to tacrolimus ointment was noted after 6 months

Group E-1: Localized and Circumscribed Brown-Black Hyperpigmented Disorder (Single to a Few Lesions)

Café Au Lait Macules

Clinical Features

Morphology

Café au lait macules (CALMs) are round to oval, smooth surface, and tan to brown macules or patches with a well-demarcated margin. Its pigmentation is uniform (Figs. 3.55 and 3.56).

Distribution

They can occur most commonly on the trunk and buttock but can be found anywhere on the body [49].

Clinical Course

Typically, they are present at birth, but appear as faint spots. By the time the child is aged 2–3 years, café au lait macules are clearly visible. They may increase in size and number with age.

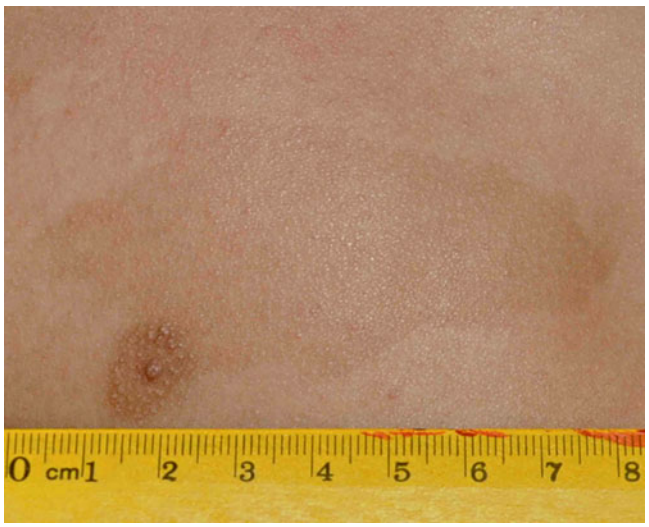

Fig. 3.55 Cafè au lait macules. This often appears as a well-demarcated *brown* macules or patches. Presence of multiple lesions is a marker for neurofibromatosis

Differential Diagnosis

1. **Congenital melanocytic nevi (CMN)**
   CMN are melanocytic nevi that present at birth. Most of them are deeply pigmented brownish macules, papules, or plaques with cobblestoned surface and coarse dark hairs. Its margin is well defined. Lesions are subdivided by size: small: <1.5 cm, medium: 1.5 cm to <20 cm, and giant: >20 cm diameter in adults (9 cm on the scalp and 6 cm on the trunk in newborns) (Figs. 3.57 and 3.58). On biopsy, it has both junctional and dermal components. It is characteristic to observe nevus cells in a single array throughout the middle and lower dermis and even extending into the septa of the subcutis along the adnexal structures. Regular follow-up is mandatory due to its malignant potential especially among the giant congenital melanocytic nevus.
2. **Nevus spilus**
   Hyperpigmented macules or papules occur in a speckled fashion on the background of a light brownish macule or patch of variable size. It may take several years for the characteristic spotted lesions to become evident. Hence, early speckled lentiginous nevi can be difficult to exclude in young infants. Larger varieties of nevus spilus may be segmental or follow Blaschko lines. Regular monitoring is advisable because of reports of cutaneous melanoma arising in nevus spilus.
3. **Segmental pigmentation disorder (SegPD)**
   It is one of the most common pigmentary birthmarks that may or may not be evident at birth, but most cases have an early age of onset. Lesions tend to remain stable over time (Fig. 3.59).

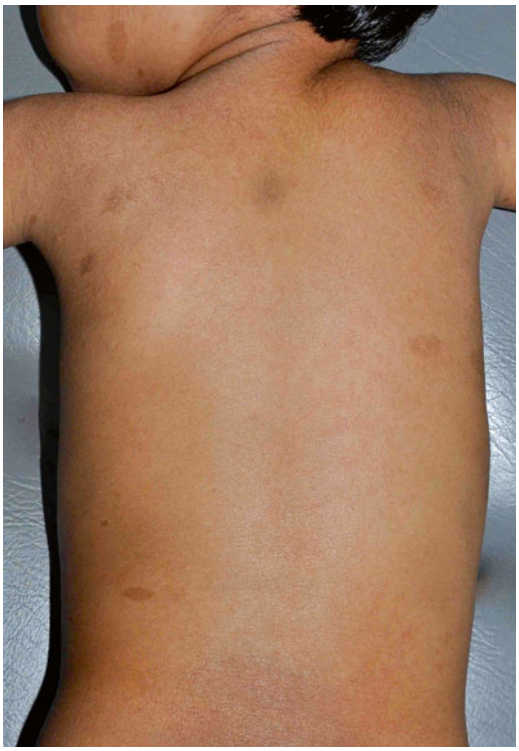

Fig. 3.56 Cafè au lait macules. This often appears as a well-demarcated *brown* macules or patches. Presence of multiple lesions is a marker for neurofibromatosis

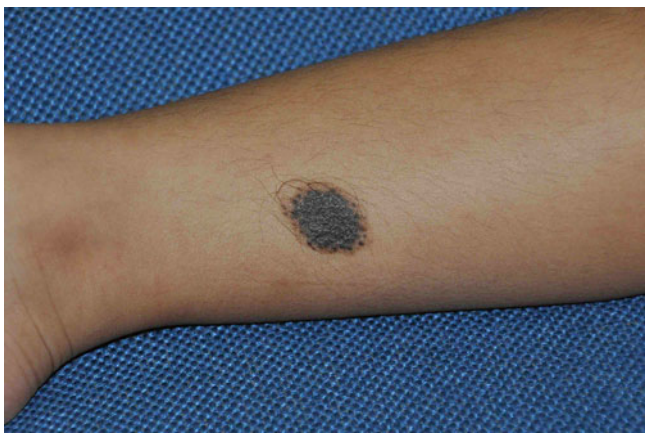

Fig. 3.57 Congenital melanocytic nevus. The nevi is *dark brown* plaque at birth with hairy surface

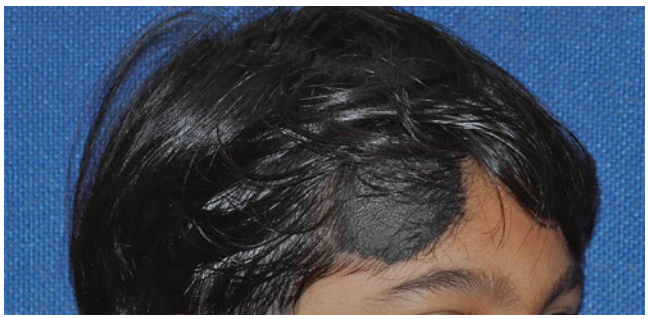

Fig. 3.58 Congenital melanocytic nevus. Large congenital melanocytic nevus on her scalp and forehead

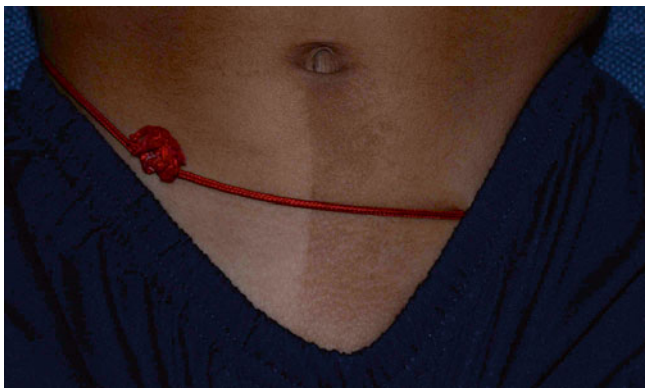

Fig. 3.59 Segmental pigmentary disorder with well-defined midline demarcation and ill-defined lateral border

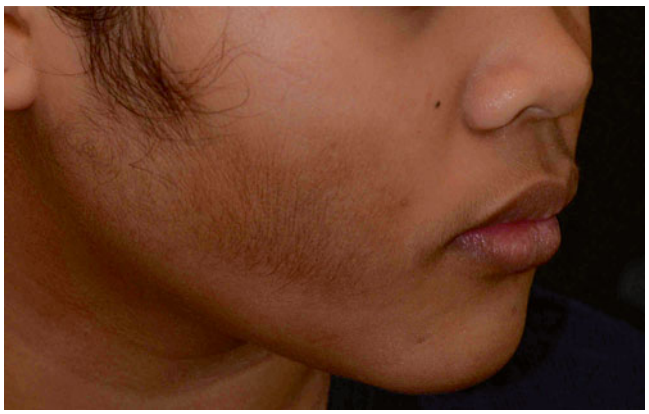

Fig. 3.60 Becker's nevus on her right cheek is shown here. A patch of uniformly pigmented skin with irregular border. Hairs within the nevus are coarser than the normal surrounding skin. It usually occurs around the deltoid region, but may occur in other parts of the body

They usually have a homogenous brown color patch that occurs in a segmental, block-like pattern, most often on the trunk, followed by the extremities, face, and neck. Sharp demarcation of lesion at the midline with a less distinctly defined lateral border is characteristic. Segmental Pigmentation Disorder may cross the midline, and it was suggested that the lesion may cross the midline a few centimeters [50].

4. **Becker nevus**

This is a congenital hamartoma that usually presents in young men as a patch of uniformly pigmented skin with irregular borders. Hairs within the nevus are coarser than the normal surrounding skin (Fig. 3.60). It typically occurs as a unilateral lesion around the deltoid region, but may occur in other parts of the body. On biopsy, the epidermis shows acanthosis with increased pigment in the basal cell layer and melanophages in the upper dermis. The number of melanocytes is normal in Becker nevus.

Diagnosis of CALMs is generally made on clinical grounds. On biopsy, CALMS have normal numbers of melanocytes with increased pigmentation at the basal layer, which readily differentiates them from melanocytic nevi. Giant melanosomes may be found. CALMs are seen

in 0.3–18 % of neonates with variation by ethnicity and race, and in 24–36 % of older children [51]. Presence of multiple CALMs is a marker of NF [52], but the macules can be sporadic or associated with a variety of syndromes (Watson syndrome, Legius syndrome, Ataxia-telangiectasia, Bloom and Albright syndrome, etc.)

Treatment

In CALMs, treatment is generally not necessary. Laser therapy can be considered in disfiguring cases, i.e., facial CALMs, but results are inconsistent. Laser treatment (e.g., Q-switched ruby, Q-switched Alexandrite, and Q-switched Nd-YAG) may be able to lighten the lesions.

Group E-2: Localized Circumscribed Blue-Gray Hyperpigmentation (Single to a Few Lesions)

Conditions under this group are characterized by the presence of melanocytes in the mid to lower dermis that gives a distinct blue-gray hyperpigmentation.

Mongolian Spots

Introduction

Mongolian spots are thought to result from arrest in embryonal migration from the neural crest to the epidermis. It is present in over 80 % of African-American and Asian babies [53].

Clinical Features

Morphology

Mongolian spots are well-defined, blue-gray or blue-black patches and their size can range from a few millimeters to more than 10 cm and can be single or multiple (Figs. 3.61 and 3.62).

Distribution

The sacrococcygeal area is most commonly affected, but lesions may occur on the buttock, trunk, and extremities.

Clinical Course

They are present at birth or early infancy and stabilize in infancy, with the majority fading before adulthood.

Histology reveals collection of spindle-shaped melanocytes scattered between the collagen bundles of the mid and lower dermis. No melanophages are observed.

Differential Diagnosis

The diagnosis of Mongolian spots is based on clinical morphology and location. Differential diagnosis includes:

1. **Nevus of Ota**

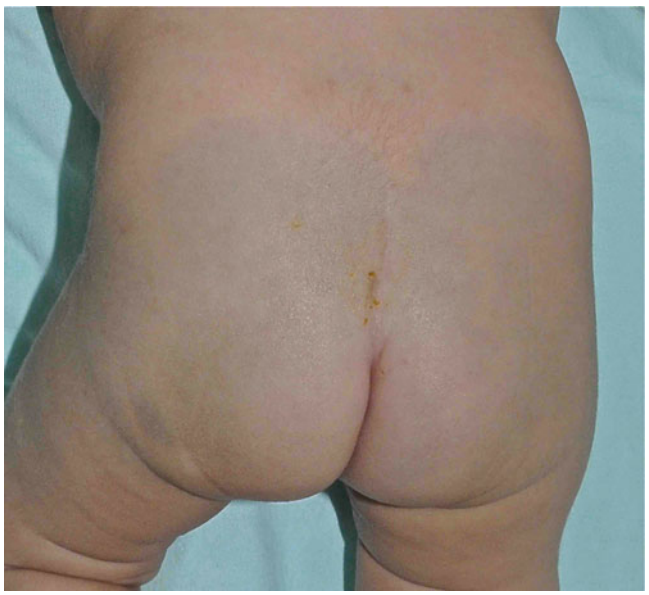

Fig. 3.61 Mongolian spots over the buttocks and lumbosacral regions of two babies with different skin types

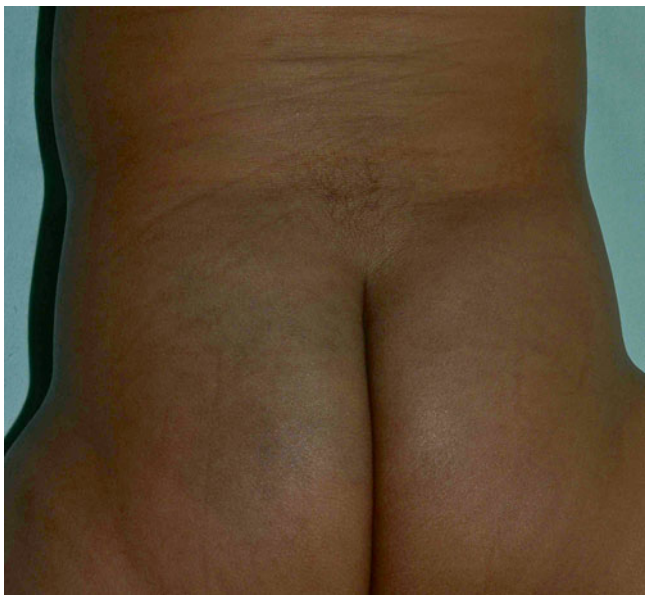

Fig. 3.62 Mongolian spots over the buttocks and lumbosacral regions of two babies with different skin types

Its typical feature is unilateral blue-gray confluent macules and patchy hyperpigmentation in the distribution of the first and second divisions of the trigeminal nerve. Bilateral involvement is described in about 5–10 % of patients.

Pigmentation of the ipsilateral sclera is common. If ocular pigmentation is present, ophthalmic assessment for glaucoma is indicated [54]. In contrast to Mongolian spot, nevus of Ota doesn't lighten with time (Figs. 3.63

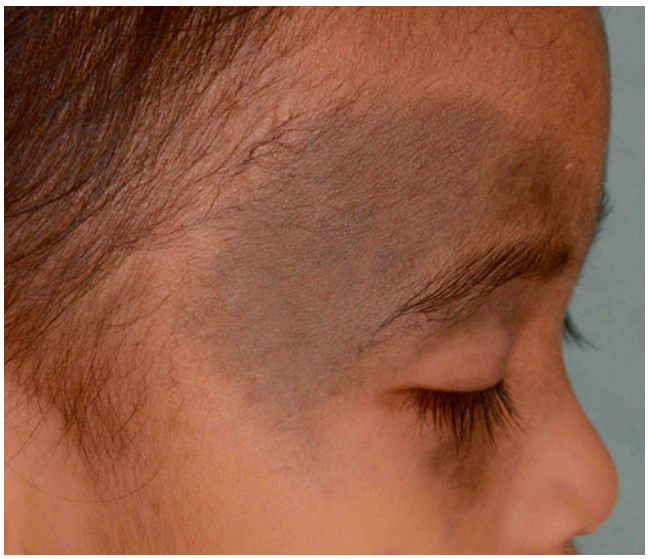

Fig. 3.63 Nevus of Ota noted since birth

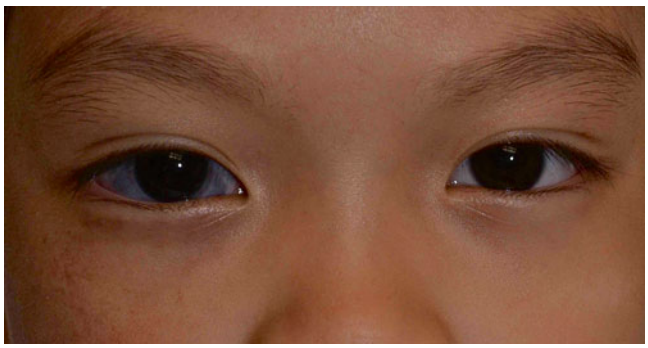

Fig. 3.64 Nevus of Ota. Unilateral *blue-gray* patch over her right face with sclera involvement

and 3.64). Q-switched lasers are helpful to improve its cosmetic outcome.

2. **Nevus of Ito**
   It has the same features as Nevus of Ota morphologically and histologically, but is located over the shoulder girdle region, usually on one side only that approximates the distribution of the supraclavicular and lateral brachial nerves (Fig. 3.65).
3. **Phakomatosis pigmentovascularis**
   When dermal melanocytosis occurs simultaneously with other birthmarks, including nevus spilus, nevus flammeus, nevus anemicus, and epidermal nevus, phakomatosis pigmentovascularis needs to be considered (Fig. 3.66).

Treatment

Most Mongolian spots will fade over time and seldom require treatment. It may sometimes serve as a marker for

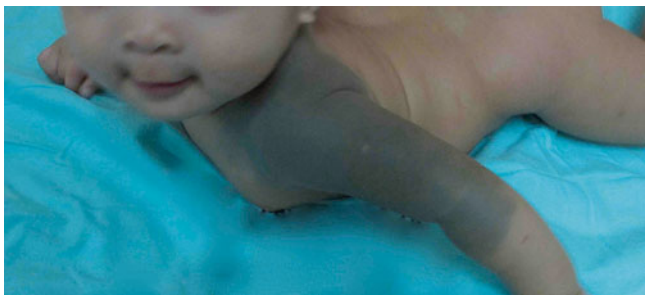

Fig. 3.65 Nevus of Ito. It presents as a large *blue to gray* patch affecting his left shoulder and upper arm since birth

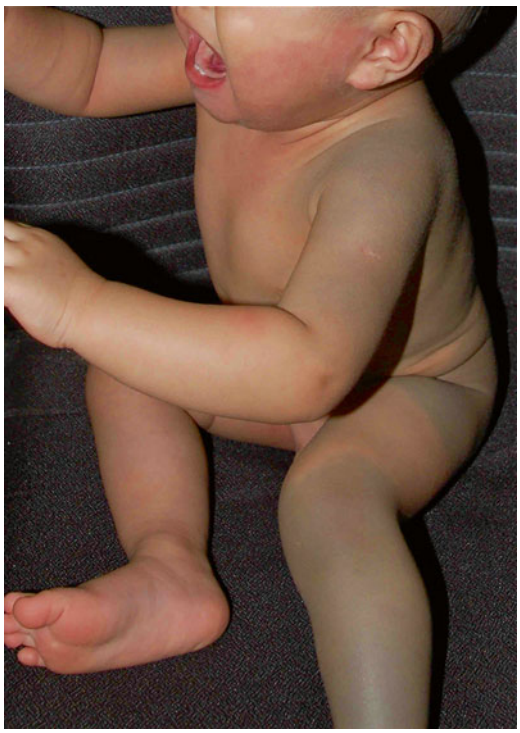

Fig. 3.66 Phakomatosis pigmentovascularis type 2a. Extensive capillary malformation on his head and dermal melanocytosis are seen

systemic diseases, e.g., lysosomal storage disease, if the lesions are persistent and extensive with indistinct borders [55].

Group F: Patterned Hyperpigmentation

A variety of hyperpigmented skin disorders as listed in group F may present in a segmental pattern or along the Blaschko lines. Hyperpigmentation along the lines of Blaschko may be seen as an isolated skin disorder or as one of the manifestations of a multisystemic genetic disorder. It is considered to be a physical representation of genomic mosaicism.

Linear and Whorled Nevoid Hypermelanosis

Introduction

Linear and whorled nevoid hypermelanosis (LWNH) is a rare entity characterized by reticulate hyperpigmented macules in a streaky configuration. It was first described in 1988 by Kalter and colleagues. The cause of linear and whorled nevoid hypermelanosis is not currently known. Nearly all have occurred sporadically; however apparent genetic transmission has been described in a few families [56, 57].

Clinical Features

Morphology and Progression

Hyperpigmented macules that are not preceded by inflammation or vesicles. Its surface is normal and non-atrophied. It usually appears within a few weeks of birth and tends to progress for 1–2 years before stabilization and usually persists indefinitely.

Distribution and Pattern (Fig. 3.67)

It can affect a localized area or an entire limb, quadrant, or the whole body symmetrically or asymmetrically. The pigmented macules follow the lines of Blaschko and display a V-shaped pattern over the spine, an S-shaped or whorled pattern over the anterior and lateral aspects of the trunk, and a linear arrangement over the extremities or genitalia. The palms, soles, mucous membranes, and hairs are typically spared.

Extracutaneous Features

Most reported cases of linear and whorled nevoid hypermelanosis have no associated abnormalities. In a retrospective study on 16 children with linear and whorled nevoid hypermelanosis, only one out of six patients with the diffuse form LWNH had autism and severe psychomotor delay. The remaining ten children with unilateral form LWNH were normal [58]. The extracutaneous abnormalities that have been observed in a number of patients with LWNH, involving mostly the central nervous, musculoskeletal systems [59–62], and also cardiac defects [63, 64].

Differential Diagnosis

1. **Incontinentia pigmenti (hyperpigmented stage)**
   Incontinentia pigmenti almost always occurs in girls and is generally fatal in boys. The hyperpigmented lesions are often preceded by vesicular and verrucous stages. The skin appendages, including hair and teeth, are commonly affected with scarring alopecia, hypodontia, and peg-shaped teeth. Histologically, there is incontinence of melanin pigment, tissue eosinophilia, and melanophages in the dermis (Figs. 3.68, 3.69, 3.70, and 3.71).
2. **Linear epidermal nevus**
   Epidermal nevi usually present as hyperpigmented streaks with hyperkeratotic or papillomatous surface (Fig. 3.72).
3. **X-linked dominant chondrodysplasia punctata**

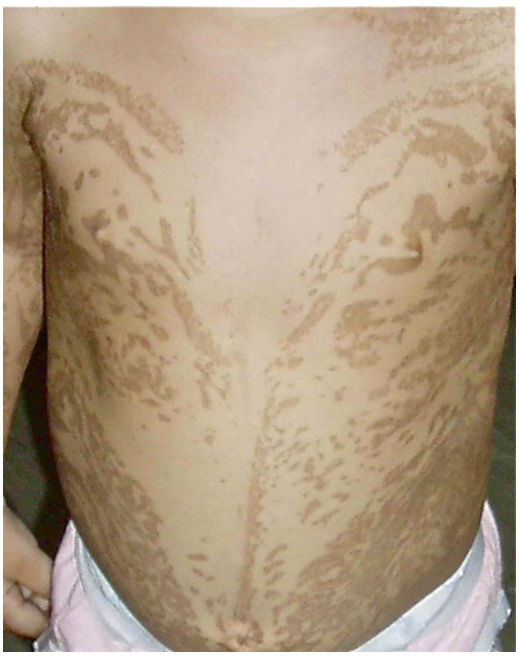

Fig. 3.67 Linear and whorled nevoid hypermelanosis. These lesions are not preceded by vesicles or inflammation

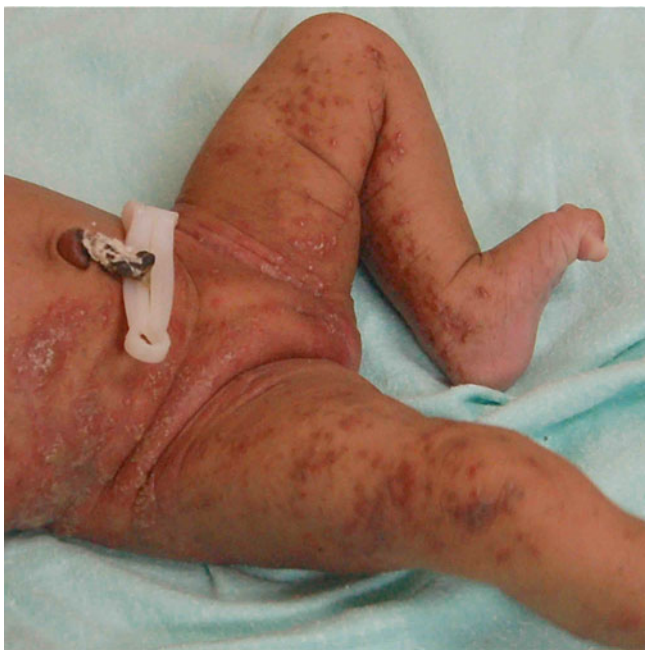

Fig. 3.68 Incontinentia pigmenti (IP). Vesicles and verrucous papules are distributed in a linear fashion on the limbs, along the Blaschko lines during her first few months of life

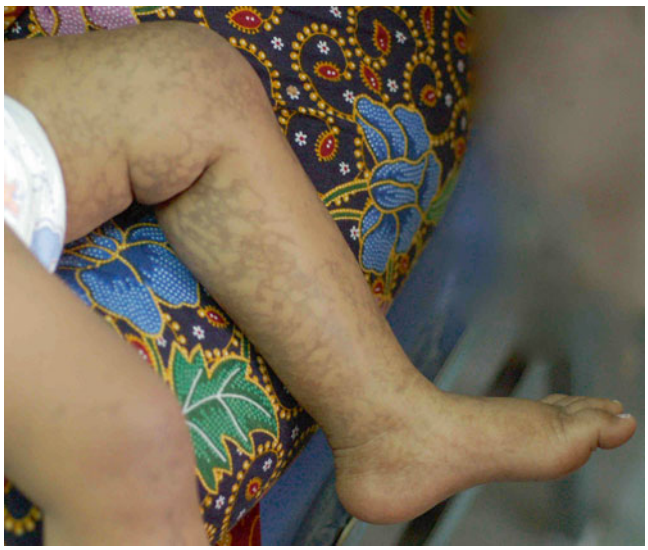

Fig. 3.69 Incontinentia pigmenti and its hyperpigmented stage. Incontinentia pigmenti has four stages: vesicular, verrucous, hyperpigmentation, and finally atrophic hypopigmentation

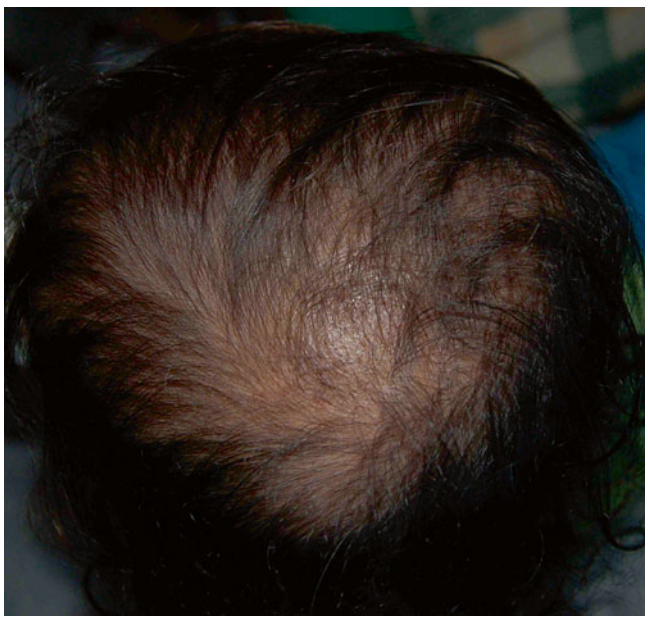

Fig. 3.70 Incontinentia pigmenti. It is an ectodermal dysplasia disorder that affects cutaneous, vertex hair loss, hypodontia, eyes, dental, cerebral, and skeletal manifestation

The early phases are erythrodermic ichthyosis with hyperpigmentation that is followed by linear scarring with follicular pitting (Fig. 3.73). Other clinical findings are alopecia, cataracts, and skeletal abnormalities. Inheritance is X-linked dominant due to mutations in the EBP gene located at Xp11.22–23.

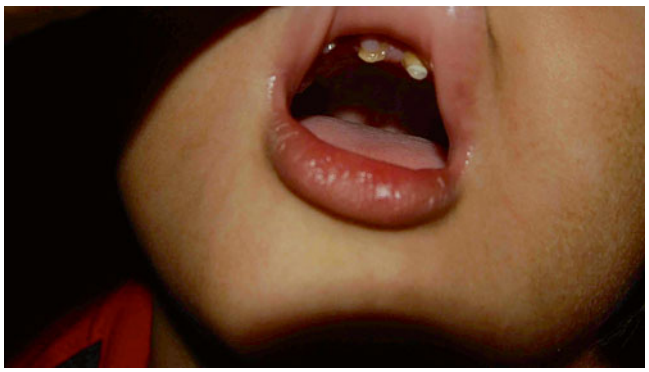

Fig. 3.71 Incontinentia pigmenti. It is an ectodermal dysplasia disorder that affects cutaneous, vertex hair loss, hypodontia, eyes, dental, cerebral, and skeletal manifestation

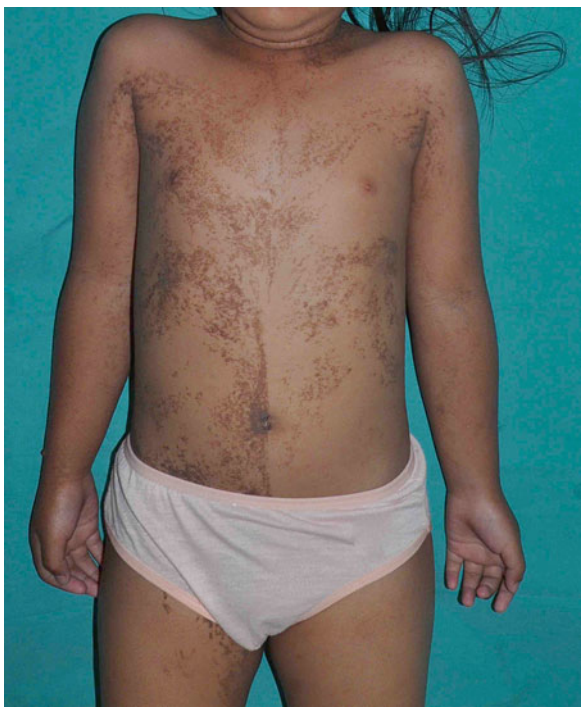

Fig. 3.72 Epidermal nevus. This young girl has hyperpigmented verrucous papules that distributed along the lines of Blaschko on her trunk and extremities

Treatment

There is no effective treatment for the skin lesions. For lesions in cosmetically sensitive areas such as the face, skin camouflage creams are a useful option. Regular follow-up to observe for delayed-onset extracutaneous abnormalities is recommended.

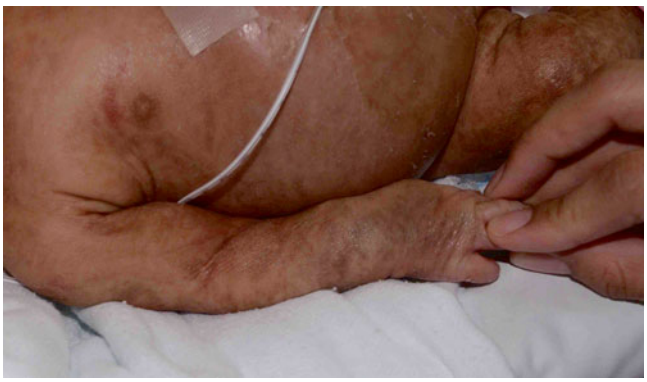

Fig. 3.73 Conradi–Hunermann syndrome. This baby has ichthyosis and hyperpigmentation along the lines of Blaschko since birth. Other findings are patchy scarring alopecia and stippled calcifications in areas of endochondral bone formation

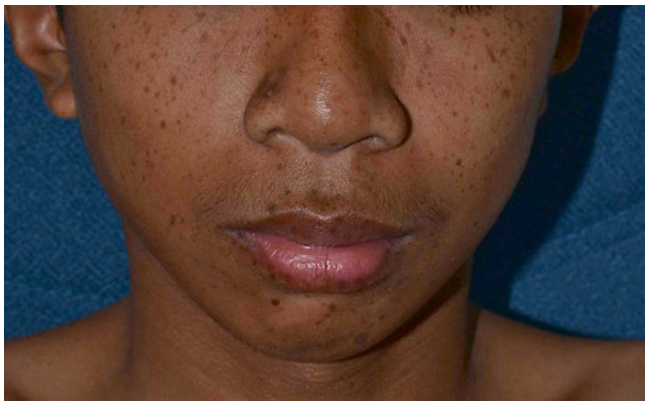

Fig. 3.74 LEOPARD syndrome. This boy has multiple facial lentigines since infantile period. Besides multiple lentigines, this boy has electrocardiographic changes, ocular hypertelorism, pulmonary hypertension, and growth retardation

Group G-1: Generalized Circumscribed Brown-Black Hyperpigmentation (Multiple)

Leopard Syndrome

Introduction

The first description of the syndrome was probably by Walther et al. in 1966, but subsequent articles by Gorlin et al. delineated the entity. LEOPARD is an acronym that includes lentigines, electrocardiographic changes, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, growth retardation, and sensorineural deafness. LEOPARD syndrome is an autosomal dominant condition with variable penetration involving multiple organs. It is due to mutation of PTPN 11 gene that encodes the protein tyrosine phosphatase SHP2 [65].

Clinical Features

Morphology

The lentigines are dark brown, irregularly shaped macules that range in size from pinpoint to 5 mm in diameter. Besides lentigines, café au lait macule can also be seen (Figs. 3.74 and 3.75).

Distribution and Pattern

They are found primarily on the face, neck, and upper trunk, with some involvement of the extremities (Figs. 3.74 and 3.75). Lesions are not limited to sun-exposed areas. The oral mucosa is typically spared [66].

Clinical Course

The lentigines may be present at birth, increasing in number until puberty.

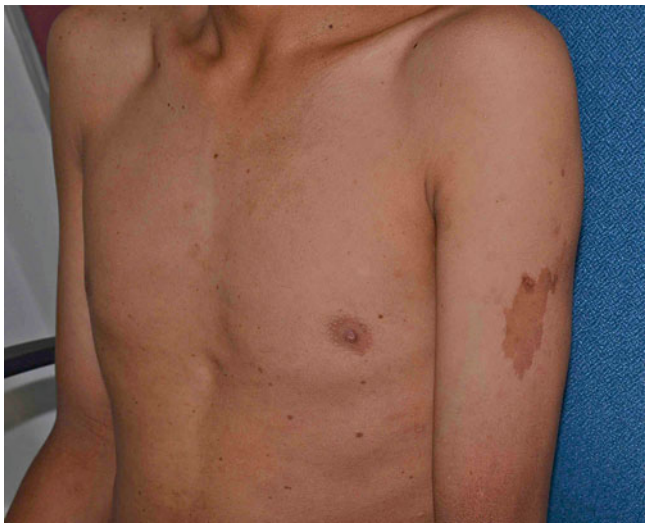

Fig. 3.75 LEOPARD syndrome. This boy has multiple lentigines on his face and body. A large café au lait spot is noted over his left upper arm

Extracutaneous Findings

All patients with multiple lentigines require complete physical examination, routine electrocardiography, echocardiogram, and hearing assessment.

A variety of extracutaneous findings with variable penetrance have been reported among children with LEOPARD syndrome that include [67, 68]

1. Cardiac: Conduction defects and pulmonary/subaortic stenosis
2. Sensorineural deafness
3. Mental and growth retardation, pectus excavatum
4. Undescended testis, delayed puberty, and gonadal hypoplasia
5. Dysmorphic facies with hypertelorism (Fig. 3.76)

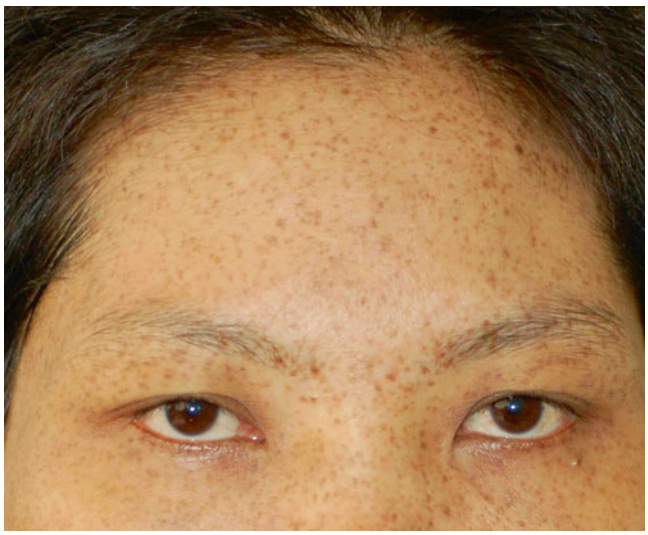

Fig. 3.76 LEOPARD syndrome with ocular hypertelorism

Differential Diagnosis

1. **Lentiginosis profusa and partial unilateral lentiginosis** [69]
   "Generalized lentiginosis" and "lentiginosis profusa" are often reserved for such patients who have widespread lentigines without associated noncutaneous abnormalities, and "LEOPARD syndrome" is often reserved for patients with systemic anomalies.

   Partial unilateral lentiginosis or "Lentiginous mosaicism" consists of clustered lentigines in a segmental form on a background of normal-appearing skin that may be present at birth or early childhood (Fig. 3.77).
2. **Carney complex**
   Clinically the lentigines are very similar to those found in LEOPARD syndrome. They are distributed diffusely on the body and are most commonly found on the face, neck, and upper trunk. The main difference is that lentigines involve the oral mucosa in Carney complex, whereas in LEOPARD syndrome, the oral mucosa is typically spared. In addition, patients with Carney complex have no dysmorphic facies.

   Other associated findings in Carney complex include blue and junctional nevi, cutaneous myxoma, atrial myxoma, endocrine disease, and testicular tumor [70].
3. **Transient pustular neonatal melanosis (TPNM)**
   During neonatal and early infancy, there may be confusion between hyperpigmented macules in TPNM and lentigines in LEOPARD syndrome. Transient neonatal pustular melanosis or "Lentigines neonatorum" is a benign idiopathic skin condition mainly seen in newborns with skin of color, has distinctive feature that is characterized by superficial pustules at birth, and evolves into areas of macular pigmentation. They occur on the chin, neck, forehead, chest, buttocks, and back, and, less often, on the palms and soles (Fig. 3.78).

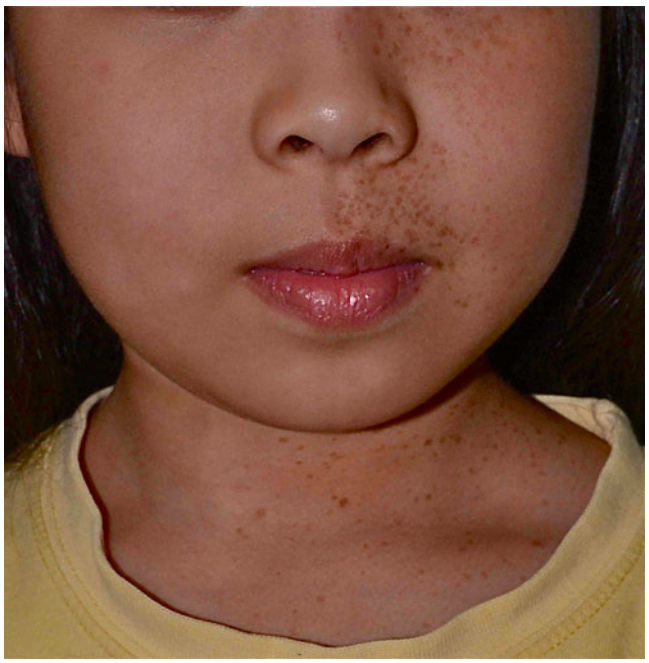

Fig. 3.77 Partial unilateral lentigines. Segmental neurofibromatosis and speckled lentiginous nevus need to be considered

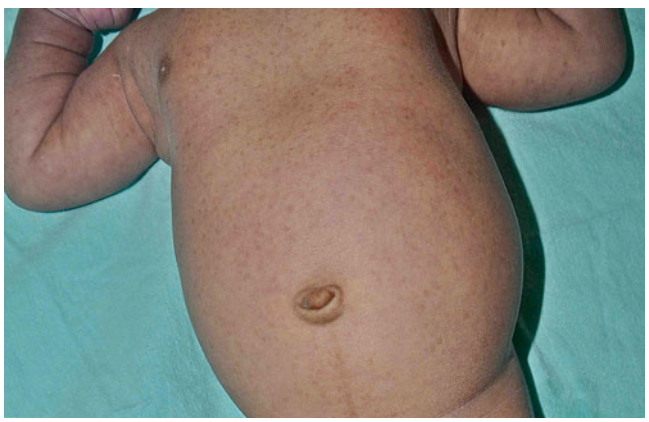

Fig. 3.78 Transient pustular neonatal melanosis with multiple *brown* macules on his body since birth

The lesions of transient neonatal pustular melanosis are always present at birth. Occasionally, only pigmented macules are present at birth, in which case the pustular phase may have occurred in utero [71]. The transient nature of brown macules that persist only for several months before spontaneous resolution is an important feature that differentiates them from lentigines in LEOPARD syndrome that persists for life.

4. **Xeroderma pigmentosum (XP)**
   XP is an autosomal recessive condition due to defective DNA excision repair mechanism. Clinical variations depend on the complementation groups.

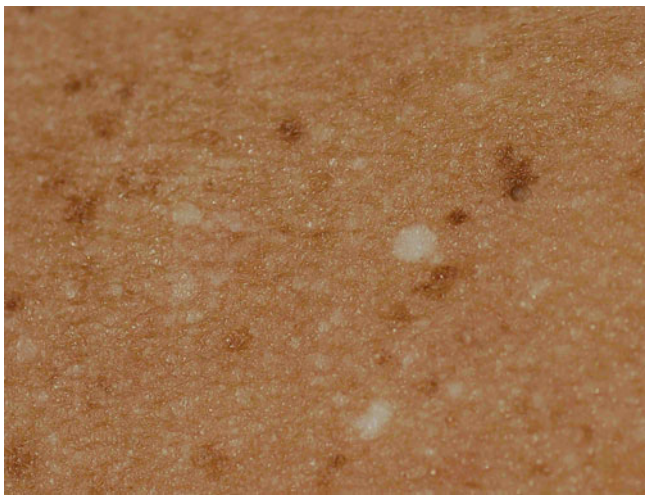

Fig. 3.79 Xeroderma pigmentosum (early stage)

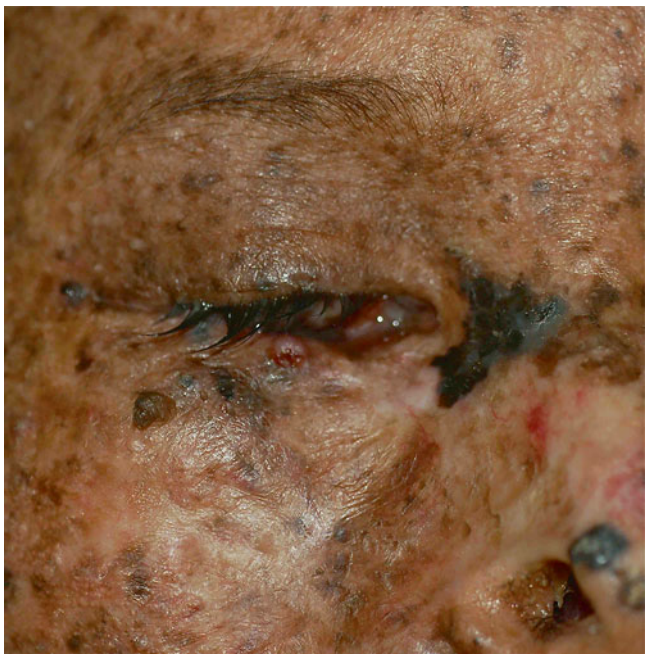

Fig. 3.80 Xeroderma pigmentosum (late stage)

The skin appears healthy at birth. Typically, the initial changes are characterized by extreme photosensitivity with diffuse erythema upon minimal sun exposure.

Soon multiple actinic lentigines of varying size develop, along with areas of mottled hypopigmentation, telangiectases, and atrophy, leading to poikiloderma at a later age (Figs. 3.79 and 3.80). Finally, multiple skin tumors may develop with age. Most common are basal cell carcinoma, squamous cell carcinoma, and malignant melanoma [72].

These lesions are seen over light-exposed areas, appearing initially on the face (Fig. 3.81). With progression of the disease, the skin changes appear on the lower legs, the neck, and even the trunk in extreme cases (Fig. 3.82)

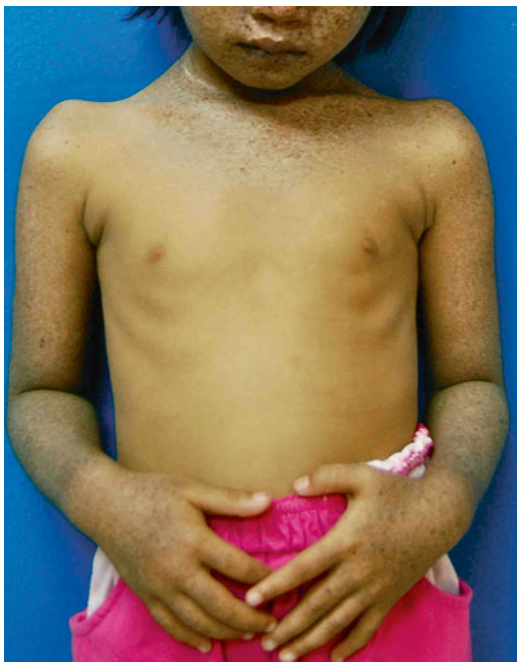

Fig. 3.81 Xeroderma pigmentosum (early stage). The mottled hyperpigmentation and atrophy were more obvious over the sun exposed areas

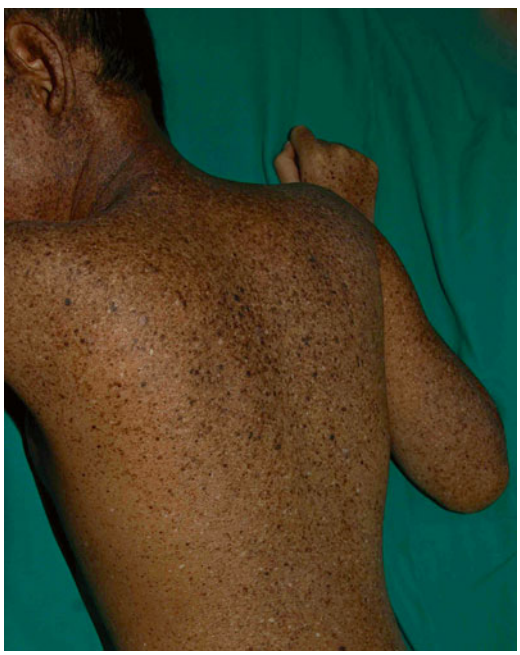

Fig. 3.82 Xeroderma pigmentosum (late stage). At later stage, the mottled hyperpigmentation and atrophy became generalized (sun exposed and protected)

5. **Peutz–Jeghers syndrome**
   Peutz–Jeghers syndrome (PJS) is an autosomal dominant inherited disorder characterized by intestinal hamartomatous

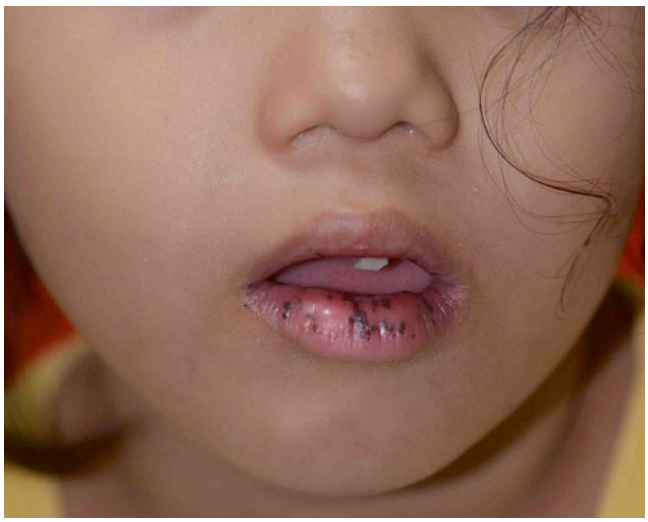

Fig. 3.83 Peutz–Jeghers syndrome. *Brown* macules noted over her lips. Labial melanotic macules are characteristic of Peutz–Jeghers syndrome. It is a cutaneous marker for gastrointestinal polyps

polyps and multiple lentigines on the lips and oral mucosa membranes.

Morphologically, they appear as small, flat, brown, or dark-blue macules similar to freckles. Most commonly around the mouth crossing the vermilion border, nostrils, perianal area, digits, and the dorsal and volar aspects of hands and feet (Fig. 3.83).

These lesions usually appear early in life but are often overlooked as freckles. They may fade after puberty but tend to persist in the buccal mucosa [73].

6. **Giant melanocytic nevus with multiple satellite lesions** Giant CMN are most common found on the posterior trunk, but can also be seen on other parts of the body. Multiple small satellite CMN are seen in the majority of patients with GCMN and often continue to develop over time (Fig. 3.84). Intradermal nevi may develop within the giant nevi as slow growing asymptomatic nodules. Patients with GCMN in a posterior axial location, especially when associated with "satellite" melanocytic nevi, are at greater risk for the development of neurocutaneous melanosis [74].

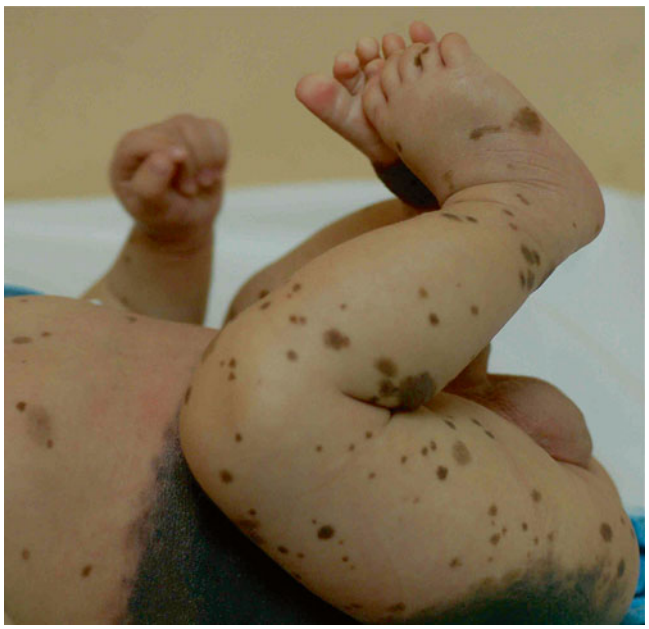

Fig. 3.84 Giant melanocytic nevus with multiple satellite lesions

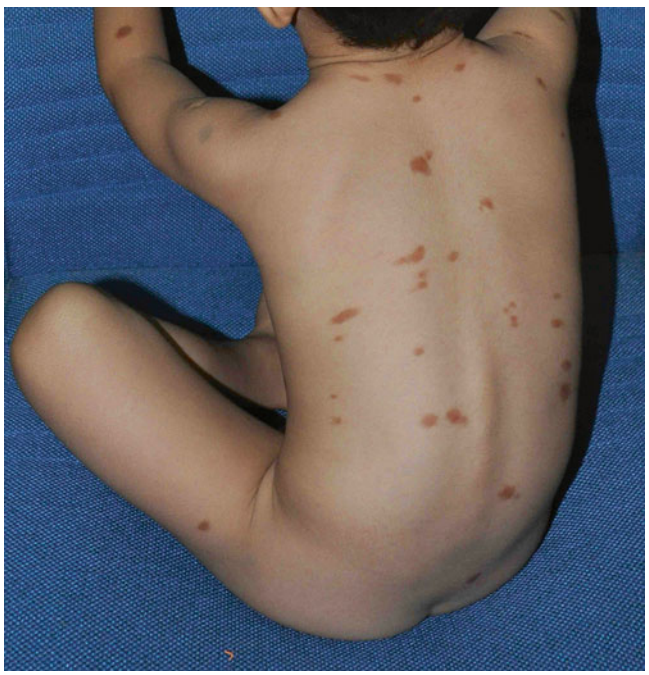

Fig. 3.85 Urticaria pigmentosa (maculopapular type). This boy had multiple well-defined *reddish brown* macules and plaque on the trunk and limbs. Most of these lesions showed positive Darier's sign

Cutaneous Mastocytosis

Introduction

The term "Mastocytosis" denotes a heterogeneous disease of bone marrow origin characterized by local or diffuse increased growth and accumulation of clonal mast cells in the skin and/or in internal organs. The skin is the organ most frequently involved and the clinical expressions of cutaneous mastocytosis (CM) are mastocytoma, maculopapular CM (formerly known as urticaria pigmentosa), and diffuse CM. Of them, maculopapular CM is the most common form and will be elaborated here.

Clinical Features

Morphology

Maculopapular CM is characterized by multiple, well-demarcated, tan to red-brown macules, patches, papules, or plaques. Occasionally, it may become vesiculobullous during flares (Fig. 3.85). The hyperpigmentation of cutaneous

mastocytosis is secondary to increased melanin in the basal cell layer and melanophages in the upper dermis.

Pattern and Distribution

There may be tens to hundreds of lesions that may occur anywhere on the skin surface. Mucous membranes may be involved, and palms and soles are usually spared.

Special Features

When a urticaria pigmentosa or mastocytoma lesion is stroked, it typically urticates, becoming pruritic, edematous, and erythematous. This change is referred to as Darier's sign, which is explainable on the basis of mast cell degranulation induced by physical stimulation.

Clinical Course

In one study, 15 % of patients had lesions at birth, and 64 % of cases were apparent by age of 6 months. Generally, the prognosis of childhood mastocytosis is favorable in most patients. According to Caplan, about half of the children with maculopapular CM will experience resolution of lesions and symptoms by adolescence, with the remainder exhibiting marked reduction in clinical symptoms [75]. When it persists into adulthood, systemic mastocytosis needs to be considered.

Diagnosis of urticaria pigmentosa may require demonstration of mast cell granules using Giemsa stain or toluidine blue stain. The hyperpigmentation of cutaneous mastocytosis is secondary to increased melanin in the basal cell layer and melanophages in the upper dermis.

Treatment

Before deciding on the treatment plan in children with cutaneous mastocytosis, the chronic clinical course of the disease and its tendency to spontaneous regression must be considered. Furthermore, systemic mastocytosis is uncommon in children.

Treatment is primarily symptomatic, as no specific therapy or cure currently exists for this disorder. If the patient is symptomatic with pruritus, urtication, and GI symptoms, the following can be helpful.

(A) H1 and H2 antihistamines, alone or in combination, are the drugs of choice.
(B) Oral sodium cromoglycate has been helpful for patients with associated GI symptoms.
(C) Topical corticosteroids are an option for symptomatic mastocytoma or selected cutaneous lesions with frequent flares.
(D) Photochemotherapy (PUVA) is an option for resistant cases among adolescents.

Avoidance of triggering factors like physical stimulation, medications, and foods must be addressed and prescription of auto-injector of epinephrine if the patient has a past history of anaphylaxis.

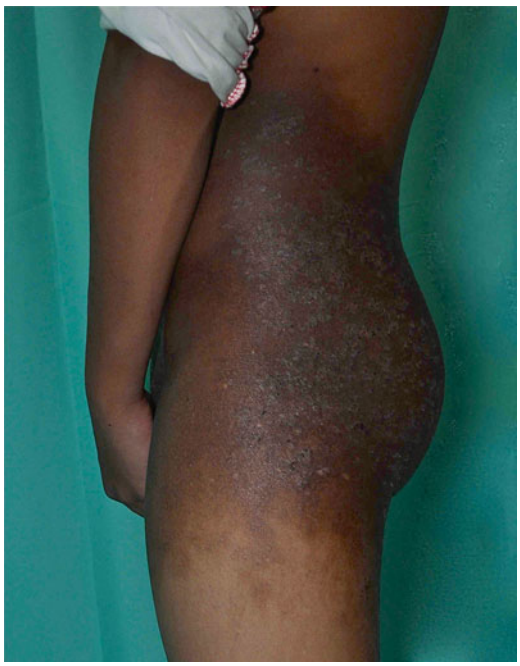

Fig. 3.86 Post-inflammatory hyperpigmentation with underlying tinea corporis

Post-inflammatory Hyperpigmentation

Post-inflammatory hyperpigmentation follows inflammatory disorders (Figs. 3.86 and 3.87) or injury. It is mostly observed in darker skin types.

Inflammation in the epidermis stimulates melanocytes to increase the synthesis of melanin and subsequently to transfer the pigment to surrounding keratinocytes.

Its manifestation (morphology, patterns, and distribution) is dependent on the primary process. If the basal layer is damaged, melanin pigment is released in the papillary dermis, where they are engulfed by macrophages. The dermal pigment looks slightly blue brown rather than a pure brown, as noted earlier. Lichen planus is a good example of this sequence (Fig. 3.88).

PIH is usually transient but may take months to years to gradually resolve.

Group G-2: Generalized Circumscribed Brown-Black Hyperpigmentation (Multiple)

Erythema Dyschromium Perstans

Introduction

Erythema dyschromium perstans (EDP) or ashy dermatosis is an acquired disorder of unknown cause that was first described in 1957 by Ramírez [76].

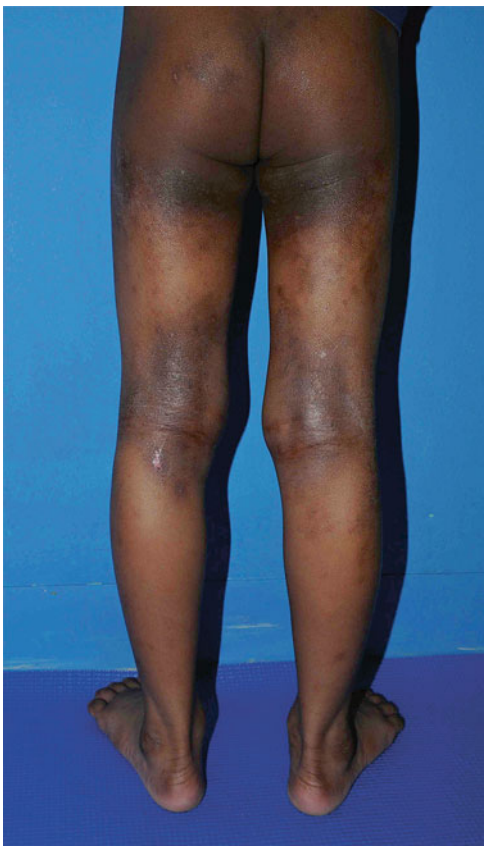

Fig. 3.87 Post-inflammatory hyperpigmentation secondary to flexural atopic eczema

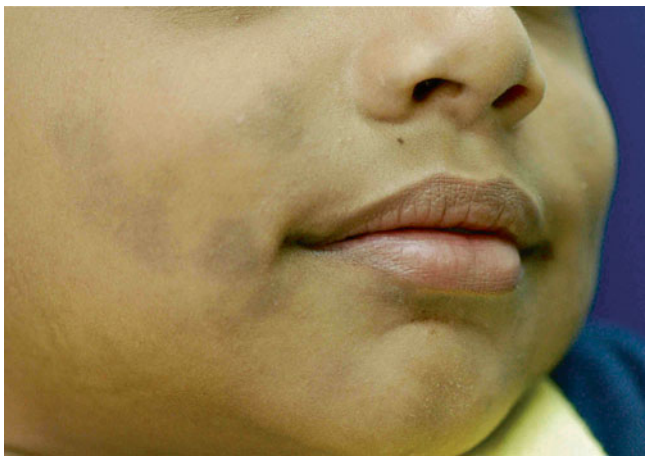

Fig. 3.88 Lichen planus pigmentosus

Morphology: It is an asymptomatic eruption of oval, circular, or irregular shaped macules and patches that are slate gray to blue brown in color (Fig. 3.89). In the early stage, there may be a thin erythematous margin.

Distribution and pattern: Initial site of involvement is often the trunk, with subsequent spread to the neck, proximal extremities, and occasionally the face. Mucous membranes are spared. The long axis of lesions may follow skin cleavage lines (Fig. 3.90).

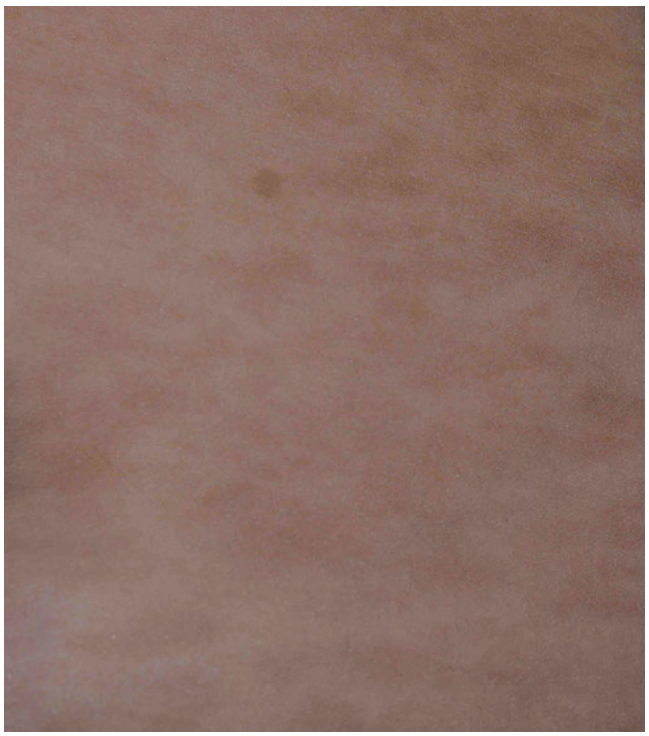

Fig. 3.89 Ashy dermatosis (close-up)

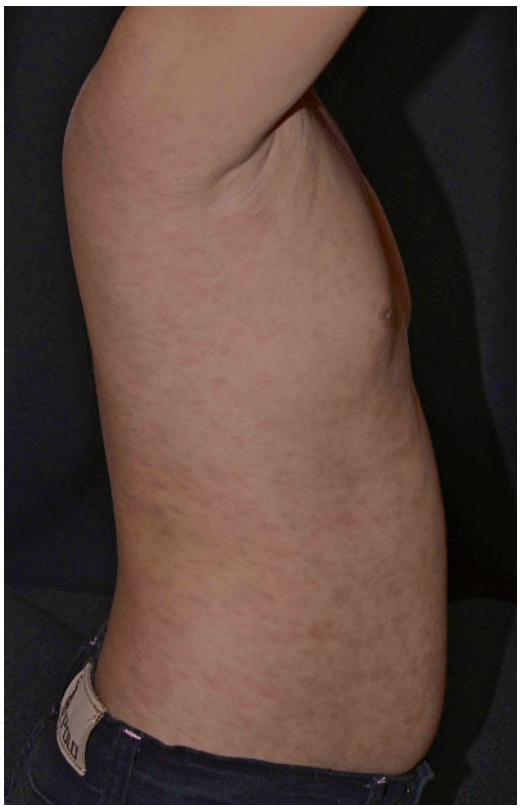

Fig. 3.90 Ashy dermatosis

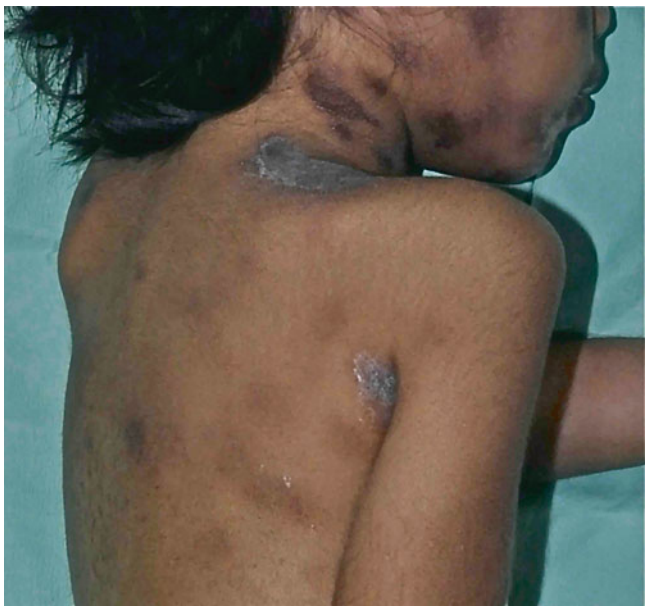

Fig. 3.91 Generalized fixed drug eruption secondary to paracetamol ingestion

Clinical course: The disease progresses slowly in symmetrical pattern. Of note, in one study of 25 prepubertal children, the disease spontaneously resolved in 69 % of the patients, with no recurrences over the following 2–3 years [77].

Skin biopsy reveals prominent dermal melanophages without visible basal layer damage. Lichenoid inflammatory infiltrate is seen.

Differential diagnoses include cutaneous mastocytosis and generalized fixed drug eruption Fixed drug eruptions (FDEs) characteristically recur at the same site or sites each time a particular drug is taken. Morphologically, the acute lesions usually develop within 30 min to 8 h of taking the drug as an erythematous, bright red or dusky red macule that might evolve into an edematous plaque with residual grayish or slate-colored hyperpigmentation (Fig. 3.91). Sometimes blisters may occur. Lesions are more common on the limbs than the trunk; the hands and feet, genitalia (glans penis), and perianal areas are favorite sites. Lesions may occur around the mouth or the eyes. They are sometimes solitary at first, but with repeated attacks new lesions may appear and progress to generalized form. Common causative drugs are paracetamol, NSAIDs, tetracycline, doxycycline, and other antibiotics.

Treatment for Ashy Dermatosis

In general, most treatment modalities including sun protection, phototherapy, topical corticosteroids, retinoids, etc., for EDP are unsuccessful. On the basis of a small case series, clofazimine was reported as a successful treatment among adults [78]. But unlike adults, spontaneous remission can occur especially among prepubertal children.

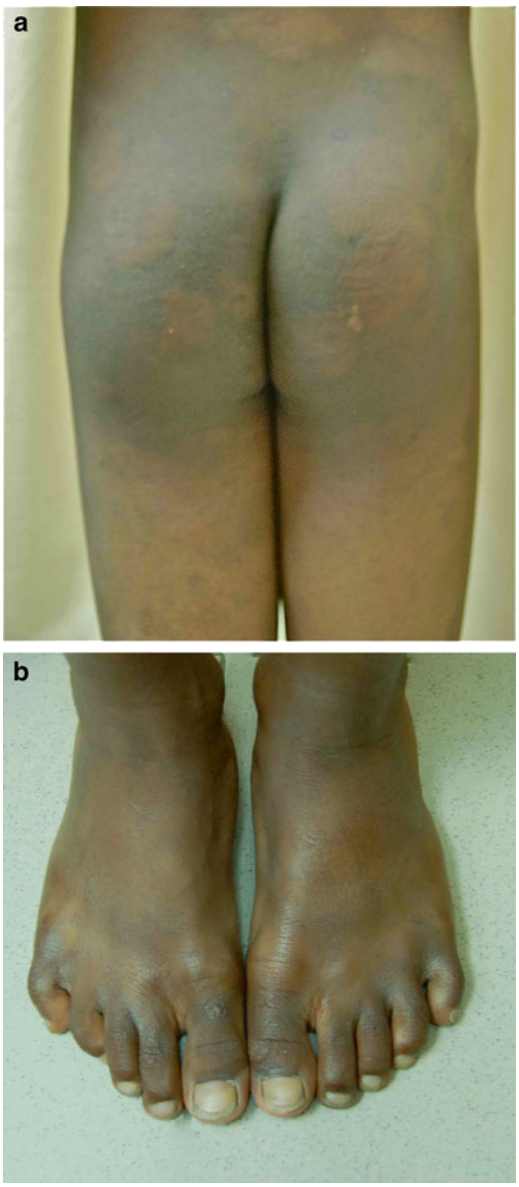

Fig. 3.92 (**a**, **b**) Clofazimine induced *blue-gray* hyperpigmentation in a child with leprosy. Gradual fading of pigmentary changes is seen with withdrawal of the drug

Group H-1: Generalized Diffuse Hyperpigmentation Without Skin Thickening or Hyperkeratosis

The underlying causes are

1. Drug induced
   Many drugs (e.g., Clofazimine, Antimalarials, and Phenothiazine) may cause localized or diffuse hyperpigmentation of the skin, nails, and mucous membranes (Fig. 3.92a, b)
2. Post-inflammatory hyperpigmentation, e.g., systemic lupus erythematous (Fig. 3.93a, b), generalized eczema, or psoriasis, etc.

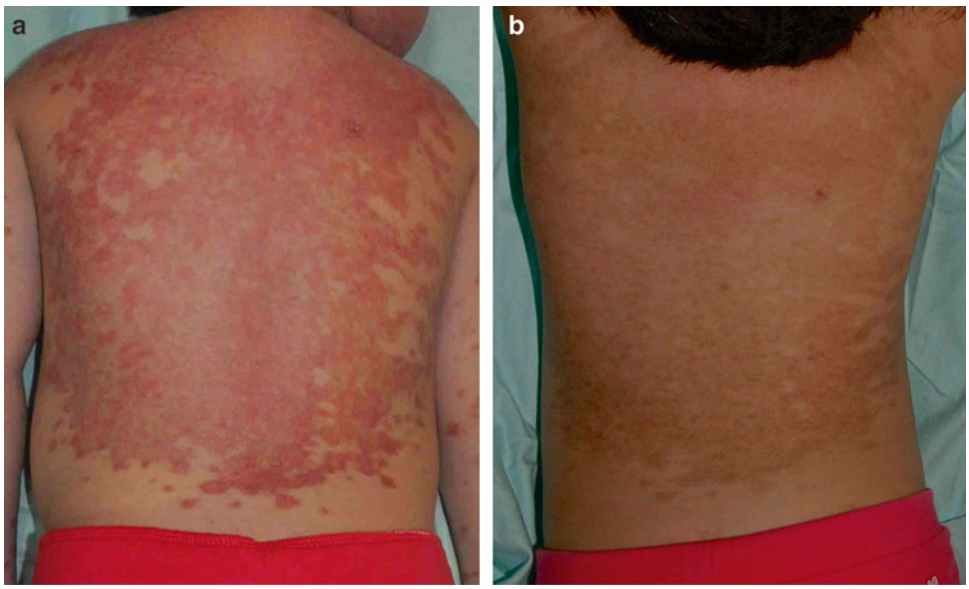

Fig. 3.93 Generalized diffuse hyperpigmentation secondary to subacute lupus erythematous (before (**a**) and after (**b**) treatment)

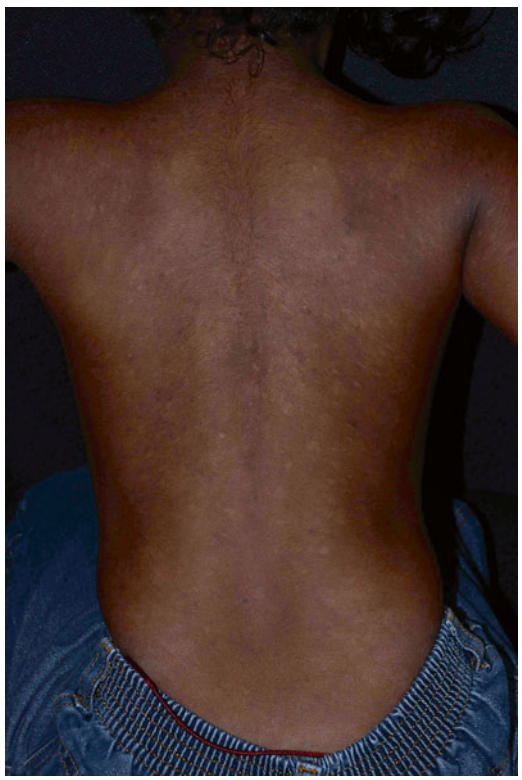

Fig. 3.94 Generalized diffuse hyperpigmentation secondary to narrow band UVB on a child with mycosis fungoides

3. Chronic renal and liver failure
4. Hemochromatosis—primary and secondary
5. Irradiation, e.g., phototherapy (Fig. 3.94)
6. Endocrine disorder, e.g., Addison disease, hyperthyroidism, or ACTH therapy.

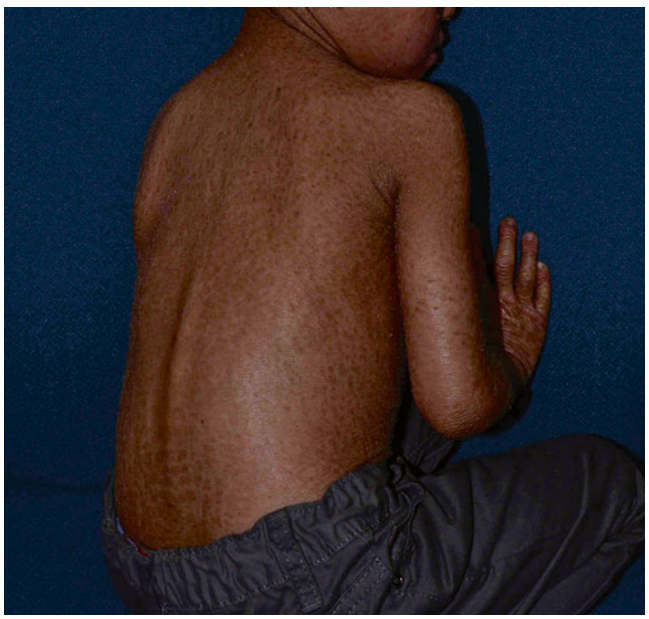

Fig. 3.95 Lamellar Ichthyosis. The scales in lamellar ichthyosis are large, *brownish* in color, plate-like with adherent center

Group H-2: Generalized Diffuse Hyperpigmentation with Skin Thickening or Hyperkeratosis

(a) Congenital ichthyosis, e.g., lamellar ichthyosis (Fig. 3.95) and epidermolytic hyperkeratosis

(b) Acanthosis nigricans
Acanthosis nigricans is a disorder that is characterized by symmetrical, hyperpigmented, velvety plaques that may occur in almost any location but most commonly appear

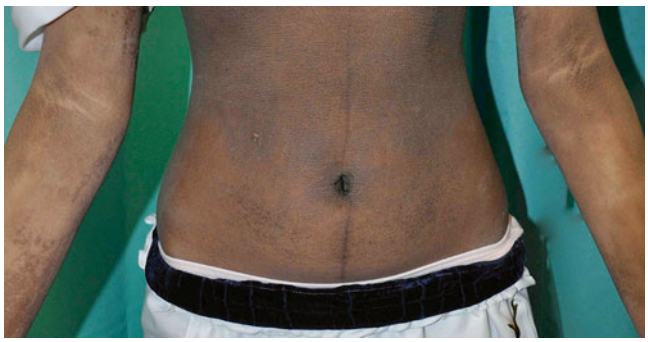

Fig. 3.96 Generalized diffuse acanthosis nigricans. It is rare and has been reported in pediatric patients without underlying systemic diseases

on the intertriginous areas. The posterior neck is the commonest site in children. Rarely, it becomes generalized [79] (Fig. 3.96). It may be familial, drug related, part of a genetic syndrome, associated with obesity, or underlying malignancy. Its presence is a reliable cutaneous marker for hyperinsulinemia and rapidly progressive extensive acanthosis nigricans with papillomatosis is often associated with internal malignancy.

(c) Exfoliative dermatitis with chronic skin changes of lichenification and hyperpigmentation (Fig. 3.97)

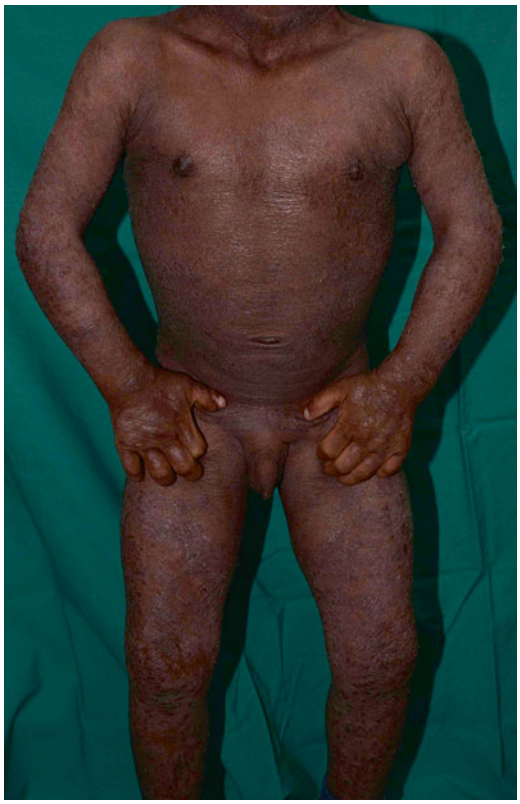

Fig. 3.97 Generalized exfoliative dermatitis. This boy shows generalized diffuse scaly hyperpigmentation and lichenification

Group I: Mixed Hypo- and Hyperpigmentation Without Atrophy

Dyschromatoses

The dyschromatoses are a group of pigmentary dermatoses featured by both macular hypo- and hyperpigmentation without atrophy. Two major forms of dyschromatoses have been described: dyschromatosis symmetrica hereditaria (DSH) and dyschromatosis universalis hereditaria (DUH).

Dyschromatosis Symmetrica Hereditaria

DSH was first reported by Toyama in 1929. It is an autosomal dominant disorder with high penetrance due to mutations in the DSRAD gene, which encodes double-stranded RNA-specific adenosine deaminase, and is detected in Japanese and Chinese families with this disorder [80].

Morphologically, there are hypopigmented and hyperpigmented macules seen over the distal extremities especially dorsal aspects of the hands and feet (Fig. 3.98a–d).Up to 70 % of them develop the skin lesions by 6 years .Often they increase in size and number till adolescence, where they stabilize, and then persist indefinitely .

Diagnosis is by the characteristic cutaneous findings and familial incidence. It should be differentiated from acropigmentation of Kitamura and early xeroderma pigmentosum.

In general, current treatments are unsatisfactory.

Dyschromatosis Universalis Hereditaria

DUH was first described in 1933 in Japan. Although most reported cases of DUH were of Japanese origin, sporadic cases have been reported from all over the world. The underlying gene defect has been linked to chromosomes 6 q24.2–q25.2 and 12q21–23. It is an uncommon disorder of unknown cause that is characterized by hypo- and hyperpigmented macules of various sizes and shapes with a mottled pattern. Lesions initially start on the trunk and subsequently generalize to head and extremities. It usually spares the mucous membranes.

Twenty percent of them had evidence of dyschromia at birth and majority by 6 years. Spontaneous remission is uncommon [81]. Differential diagnoses are chronic arsenic poisoning, xeroderma pigmentosum and dyschromic amyloidosis cutis (Fig. 3.99), and dyskeratosis congenita. On biopsy, a focal increase or decrease in melanin pigment at basal layer is seen in the hyperpigmented and hypopigmented areas, respectively. No satisfactory treatment is available.

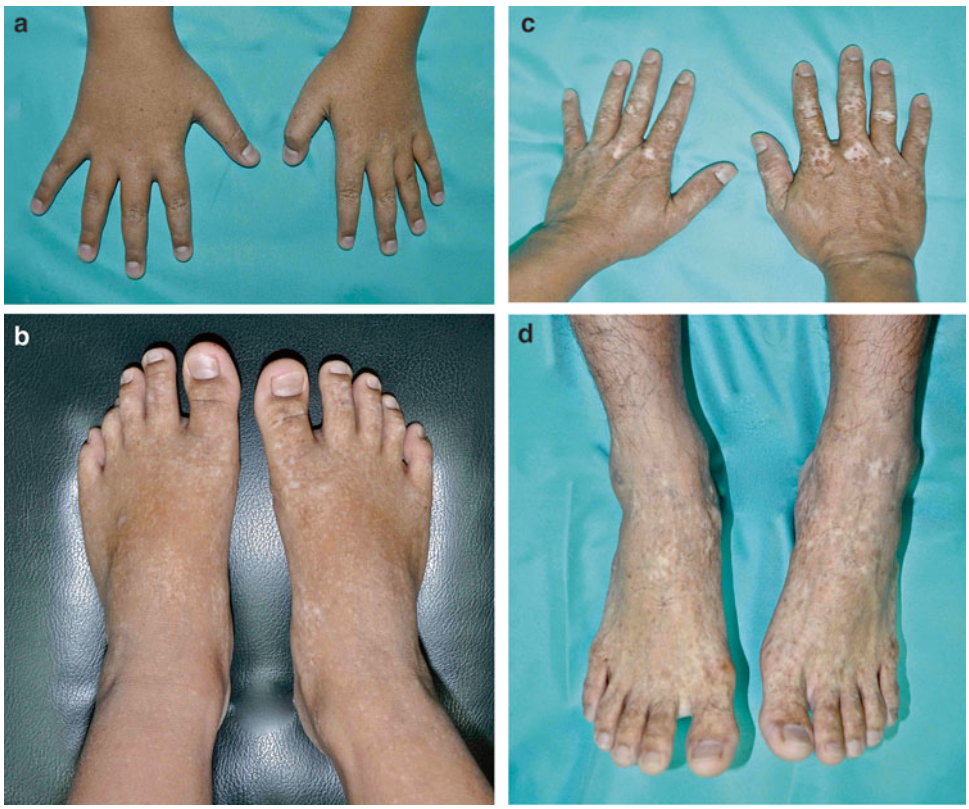

Fig. 3.98 Dyschromatosis symmetrica hereditaria (**a**, **b**: son's hands and feet/**c**, **d**: father's hands and feet). Both father and son have mixed hypo- and hyperpigmentation macules symmetrically over the dorsal aspects of their distal extremities

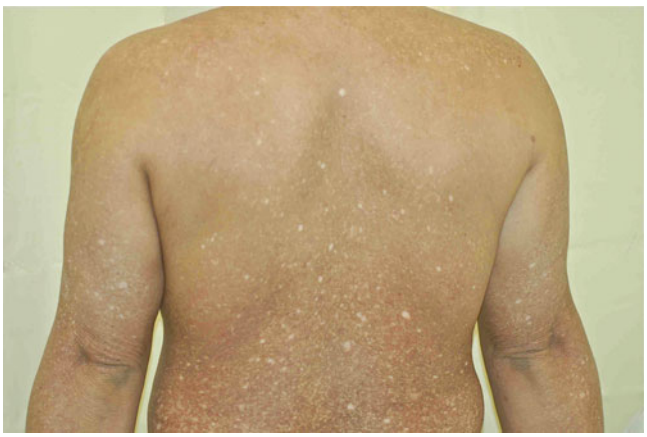

Fig. 3.99 Dyschromic amyloidosis cutis with generalized multiple hypo- and hyperpigmented macules since early childhood. Skin biopsy reveals multiple amyloid deposits with *Congo red* stain at upper dermis

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Part II

Pigmentary Conditions in Children of Color

Normal Color Variations in Children of Color

4

Nanette B. Silverberg

Abstract

Pigmentation is present in the skin, hair, nails, and mucosal surfaces in all individuals; however, variation exists in the pigmentary distribution and the prominence in pigmentation by location. Such variations are more notable in children of color due to the prominence in pigmentation. This chapter reviews the subtle differences in pigmentation noted in children of color most of which occur in the first 2 years of life. These differences in color may be based on the pattern of pigmentary and embryological development or due to environmental factors such as trauma.

Keywords

Pigmentation • Mucosal surfaces • Embryological development • Trauma

Introduction

Children of color have an extensive rich pigmentation that varies from Caucasian children by the amount and distribution of melanin in the skin. This section looks at normal variations in pigmentary development usually noted in the first 2 years in children of color.

Fitzpatrick Phototyping Scale

Fitzpatrick developed a grading system by which individuals could be divided in terms of their visual pigmentation and their response to ultraviolet injury. The division of pigmentation he created was later modified to better differentiate darkly pigmented individuals. The application of the Fitzpatrick system to racial and/or ethnic groupings is noted in Table 4.1, on the next page [1]. Children of color usually develop the majority of their pigmentation by age 2; however, evolution of pigmentation may occur throughout a lifetime.

Normal Skin in Children of Color

- **Newborns of color often have hyperpigmentation of the genitalia.**
- **The Mongolian spot is frequently noted in newborns of Black, Asian, and Hispanic descent.**
- **Patterned pigmentation including pigmentary mosaicism, café au lait macules, and nevus depigmentosus typically develop in the first 2 years of life.**

Newborn Caucasian children are lightly pigmented with light colored vellus hairs and indeterminate eye color; children of color will have only partial pigmentation at birth with darker lanugo hairs (especially Hispanic and Latino) and eye color, which may not further change with development. Cutis marmorata, a vascular pattern in the extremities which disappears with warming, may be more notable in lightly pigmented children. When very extensive at birth in children of color, this can represent a form of neonatal lupus erythematosus. Milia, sebaceous hyperplasia, and neonatal acne are common in all skin tones, races, and ethnicities. Transient

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Table 4.1 Typical reaction patterns of the skin and hair noted by race and ethnicity

Race/ethnicity	Fitzpatrick types	Skin reactions
Asian/East Asian	II–IV	Risk of sun damage, dyspigmentation/melasma, facial sensitivity, and keloids
Black/African American/ Afro-Caribbean	IV–VI	Risk of dyspigmentation, especially hyperpigmentation Obfuscation of diagnosis due to pigmentary alterations Xerosis Keloids and traction/styling related hair damage hair damage
Caucasian	I, II (rarely III)	Risk of phototoxic reactions, damage, and vascular reactivity in response to trauma and ultraviolet light exposure
South east Asian/Indian	III–V	Risk of pigmentary disturbance, especially hyperpigmentation and hypopigmentation Xerosis
Hispanic/Latino	II–V	Risk of dyspigmentation, both hyperpigmentation and hypopigmentation, obfuscation of diagnosis due to pigmentary alterations, xerosis, traction-related hair damage, keloids, and photodamage
Native American	II–IV	Risk of dyspigmentation, both hyperpigmentation and hypopigmentation, xerosis, obfuscation of diagnosis due to pigmentary alterations, and photodamage
Middle Eastern	III–VI	Risk of dyspigmentation, both hyperpigmentation and hypopigmentation, xerosis, obfuscation of diagnosis due to pigmentary alterations, and photodamage

Revised from Silverberg NB. Atlas of Cutaneous Biodiversity. Springer 2013

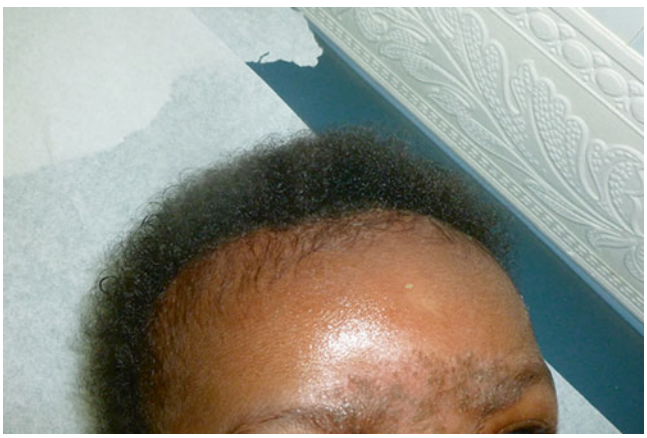

Fig. 4.1 Dark scales in a dark infant with seborrheic dermatitis

neonatal pustular melanosis, which can leave extensive spotty pigmentary alteration in black infants, is more likely to be noted at birth in children of color. The scales of infantile seborrheic dermatitis will likely be pigmented in pigmented children (Fig. 4.1). Congenital hairy pinnae may be noted in newborns of diabetic moms or children with hyperinsulinism, but is also seen more frequently in the South Pacific, India, Sri Lanka, and Africa [2].

Hyperpigmentation is noted at birth or within the first few days of life in black/African-American and Afro-Caribbean children including pigmentation of the lips, fingertips, genitalia (especially in the midline), nipples, umbilicus, axillae, and anal orifice. Pigmentation persists in most areas, except the axillae, and the rest of the body will eventually develop further pigmentation to match these sites. Only axillary hyperpigmentation disappears by the end of the first year [3]. Scrotal to perineal hyperpigmentation including peri-anal is notable in most male Black infants at birth, becoming more prominent as pigmentation develops in the first 6–12 months of life.

Pigmentary development is brisk in the first 2 years of life, obviating any underlying pigmentary mosaicism, café au lait spots, and nevus depigmentosus. During this stage of rapid pigmentary development, children of Black and Hispanic/Latino descent have more pigmentary lability with extensive hypopigmentation developing in response to insults, such as seborrheic dermatitis and/or atopic dermatitis. Eventually, with age, hyperpigmentation in response to atopic dermatitis will become the predominant pigmentation response to irritation for most children who are Black or darker Hispanic/Latino.

The Mongolian spot is a benign self-resolving pigmentation of newborns. The infants affected are generally over 2,500 g and usually 35 weeks of gestation or greater. The Mongolian spot is a bluish-gray pigmentation which develops due to the presence of melanocytes in the dermis. Whether these melanocytes are in the process of migration or local factors stimulate their accumulation (e.g., flexural positioning in utero) remains unknown. The dermal melanocytes create a Tyndall effect, which is a blue coloration due to pigmentary filtration. Mongolian spots are noted primarily at birth, but can appear up to a month later. The leading location is the sacrum and gluteal region and these lesions are rarely paired with port-wine stains in the phakomatosis pigmentovascularis type II. The Mongolian spot is a normal variant in children of color, found in 9.5–18.9 % of Caucasian infants, 46 % of Hispanic/Latino, 62.2 % of Indian, 83.6 % of Asian, and 96 % of Black newborns [4–6]. Eccentric lesions outside of the sacrum can be noted. Rarely, extensive lesions can be seen in the setting of a mucopolysaccharidosis such as Hunter's or Hurler's disease.

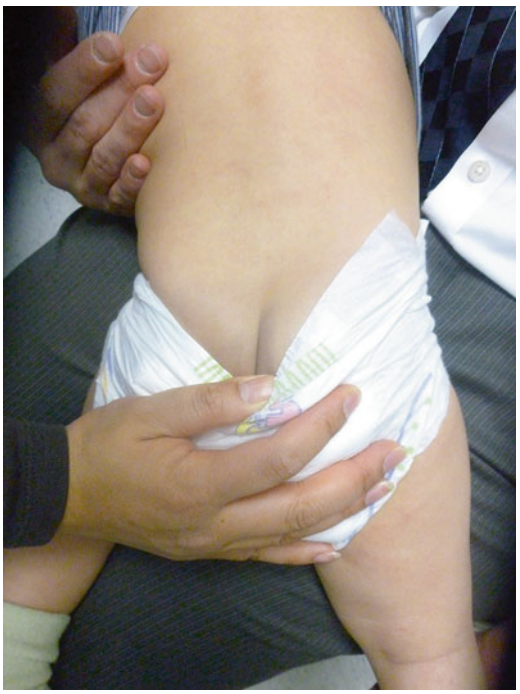

Fig. 4.2 Mongolian spot over the sacrum

One can note eccentric mongolian spots/lesions over the chest, abdomen, and extremities, notably sparing the umbilicus and breast tissue. On the extremities, lesions will be noted over the extensor surfaces (especially proximally). Resolution over the first few years of life is typical, but occasional persistence into adolescence will be noted [7, 8].

Café au lait macules (CALM) are localized post-zygotic gene mutations affecting pigment production. Darker ovoid pigmentation is a result of giant pigment granules and the presence around keratinocyte nuclei of melanosome complexes [9]. The presence of a CALM is statistically more common in black children under the age of 5 years than in Caucasian children of the same age range; the prevalence of café au lait in black vs. Caucasian children is for one lesion (22 % vs. 11 %) or two lesions (5 % vs. 2 %), respectively [10]. One of the diagnostic criteria of neurofibromatosis type I is 6 or more CALM of 5 mm+ in children or 15 mm+ in adults; however, neurofibromatosis is not more common in Black children.

Six or more CALM is the leading cutaneous marker of Neurofibromatosis type I (Fig. 4.3) [11]. McCune Albright syndrome can also be associated with a large segmental CALM, distributed over a large cutaneous surface area of the central chest or abdomen. CALM are usually one to two Fitzpatrick types darker than the skin tone of the observed individual. While there may be delayed appearance, most uncomplicated CALM are noted within the first 5 years of life, with slight delay in appearance for Black children due to lack of early pigmentary maturation. Fitzpatrick type VI

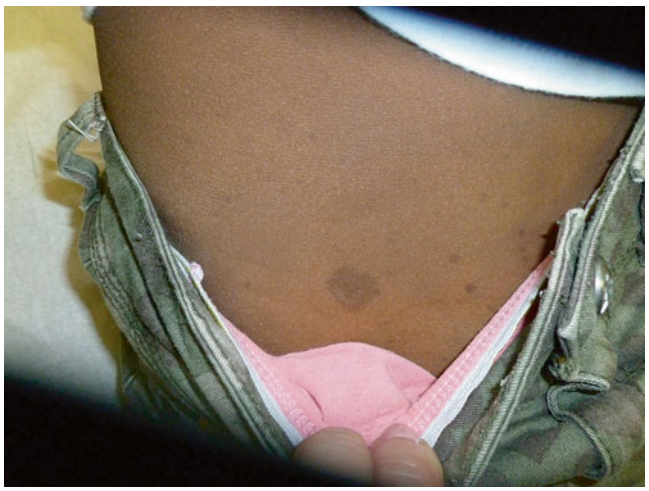

Fig. 4.3 Multiple café au lait over the back. A child with these many lesions should have a thorough family history, physical, neurological and developmental examinations as well as ophthalmologic evaluation to identify a second criterion to establish the diagnosis of neurofibromatosis type I

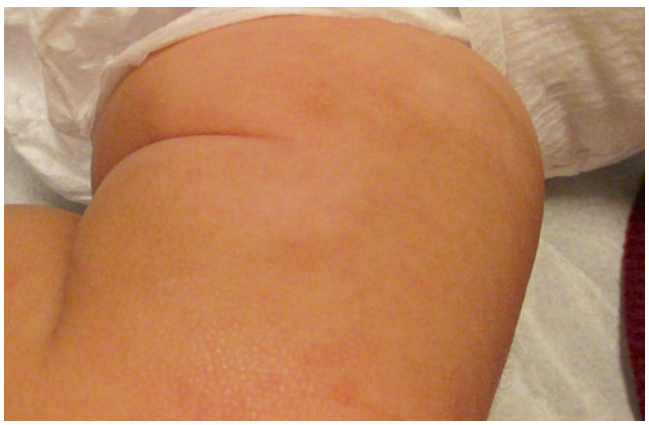

Fig. 4.4 Segmental hypopigmentation of the inner thigh in an infant consistent with nevus depigmentosus

patients may have such dark café au lait lesions as to require dermoscopy to rule out a pigmentary network of a congenital melanocytic nevus.

Ovoid hypopigmentation is more common in children of Hispanic/Latino, Indian, and Asian descent (Fig. 4.4). The nevus depigmentosus is a misnomer, as there is only a reduction of pigmentation, not an absence of pigmentation in these lesions. Sun protection may aid in avoidance of further exacerbation of the pigmentary differences. In these lesions localized increased pheomelanin to eumelanin ratio and reduced melanosome number with clumping occur. The appearance of the nevus depigmentosus when present, will be noted at birth for 50 % and almost all have formed by 1 year of life, primarily over the chest, abdomen, and extremities [12]. Overlying blond vellus hairs may be noted in light lesions of Fitzpatrick types I–III skin. Wood's lamp examination is

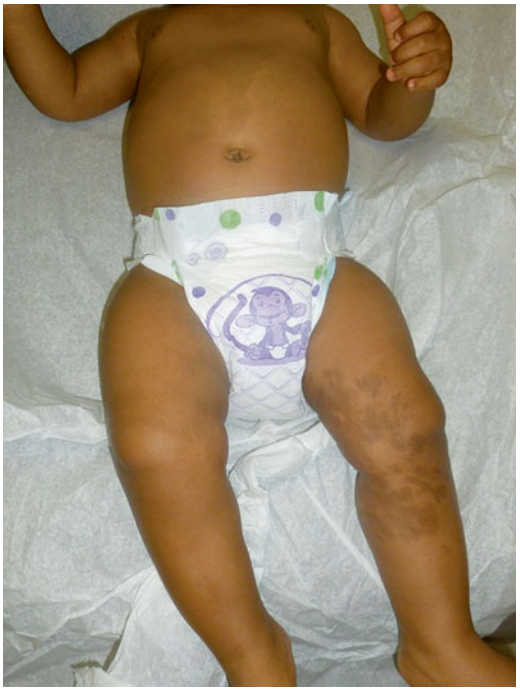

Fig. 4.5 Segmental hyperpigmentation on the upper chest and a smooth muscle hamartoma on the left lower leg

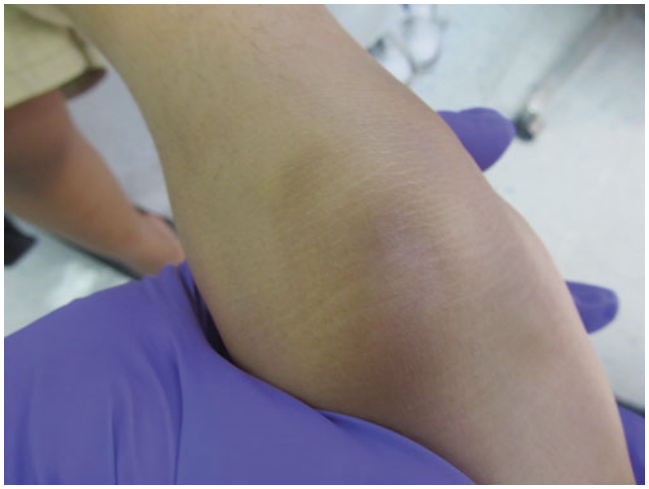

Fig. 4.6 Frictional hyperpigmentation over the ankles in an African-American child who wears hightop sneakers

negative for highlighting, distinguishing the lesions from localized or segmental vitiligo [13]. Like CALM, single lesions are common, but many lesions may suggest a syndrome such as tuberous sclerosis. Three ash leaf-shaped lesions are a major criterion for this autosomal dominant disorder. Other possible conditions include pigmentary mosaicism when the lesions are distributed in the lines of Blaschko and chimerism. Clinical correlation is needed regarding the need for further genetic work-up [12]. One-third of children with multiple lesions of hypopigmentation along the lines of Blaschko will have hypomelanosis of Ito [12].

Acral lentiginosis is a clustering of freckles or speckles over the dorsal hands and/or feet noted to be especially prominent in Indian and Black children. Head, neck, and central speckling can also be noted in such individuals. This condition should be differentiated from generalized lentiginosis of Leopard syndrome, Carney complex, and Peutz–Jegher's syndrome (see Chap. 1).

Segmental hyperpigmentation (Fig. 4.5) over the central chest, back, and proximal extremities can be seen in smooth muscle hamartomas or Becker's nevus, the former being congenital and the latter with pubertal onset. Becker's nevi are more prominent if not more common in Black patients. In these lesions the overgrowth of smooth muscle and hair accompany pigmentation. Syndromes of associated findings can be seen including associated breast hypoplasia and hemi-maxillary enlargement [14, 15] (see also P. 43).

For patients of color, pigmentation is noted in areas that are perceived to have no pigmentation in Caucasians. In Black, South Asian, and Hispanic patients, the palms and soles may be tan to light brown. The mucosal surfaces, especially the gingivae, are usually pigmented lightly as well as either diffusely (e.g., gingivae) or discretely (e.g., fungiform papillae of the tongue) [16], although this phenomenon is most prominent in South East Asia and Black patients. Such changes are normal for patients of type IV–VI skin tone. A localized tan-brown pigmentation extending onto the gingival mucosa and lip adjacent to a café au lait has been termed the split café au lait and refers to development at a time prior to oral cavity invagination in utero [17]. The differential diagnosis of excessive oral pigmentation includes Addison's disease, iron deficiency, melanoma, scleroderma, and hemochromatosis, but work-up is unnecessary unless abrupt onset is noted [18–20]. When a new area of hyperpigmentation develops in the oral mucosa in response to trauma it is termed an oral melanotic macule. This can appear congenitally like a cafe au lait, but in older patients who acquire such lesions, observation and/ or biopsy may be warranted in these situations.

Development of new pigmentation in response to trauma is also a common phenomenon in the skin as well as the mucosae. Hyperpigmentation in Black patients may result from brisk melanophage activity and the effect of release of larger melanosome/melanin packet diffusion into the dermis. One such type of pigmentation that has been described recently is bi-frontal pigmentation which has onset before the age of 2 years and demonstrates forehead post-inflammatory pigmentary alteration on biopsy but can persist indefinitely [21]. Pigmentation of the forehead can

Table 4.2 The system of pigmentary demarcation

Type A: Voigt's or Futcher's lines: Anterior pectoral region and/or inner arms (hyperpigmented)
B: Posterior medial lower extremity (hyperpigmented)
C: Hypopigmentation of the central chest or abdomen vertically oriented over the pre- or para-sternal area (hypopigmented)
D: Posteromedial area of the spine (hyperpigmented) or curved convex line on face (hyperpigmented)
E: Line from mid-third of clavicle to the areola, bilaterally (hypopigmented)

also be noted in Arab and South Asian children, especially older adolescents from devout prayer involving bowing and placing one's forehead against a rug. A callosity may accompany this lesion. Frictional hyperpigmentation can also be noted from being overweight (inner thighs) and over the ankles from shoes (e.g., hightops) (Fig. 4.6). Lichenoid atopic dermatitis features can accompany such frictional changes.

The skin cleavage lines are called Langer's lines. Melanocytes mesh within these lines, and orientation of procedures with these lines will result in enhanced scar appearance and pigmentary improvement in patients of color [22]. The patterns of skin pigmentation usually demonstrate more pigmentation on ventral than dorsal surfaces, with most Black females demonstrating such demarcation, and only 15 % of Caucasians having similar appearance [23]. Forty-six percent of female Black neonates and 16 % of Black male neonates have pigmentary demarcation visible with A and B being most commonly noted (Table 4.2). Seventy-nine percent of adult Black females will have pigmentary demarcation notable on physical exam, with A or B seen in 50 % and pregnancy promoting type B pigmentation (onset in 14 % during pregnancy). Sixty-three percent of Black females (A 36 %, B 0 %, C 45 %, D 0 %, E 1 %) and 87 % of Black males (A 50 %, B 0 %, C 25 %, D 0 %, E 19 %) demonstrate pigmentary demarcation. Seventy-five percent of Black males have pigmentary demarcation lines with type C being the most common [23]. A linea nigra is a pigmented line along the midline lower abdomen, noted in 31.4 % of children aged 0–15 years in Nigeria. Almost half of Nigerian adolescents and young adults will demonstrate a linea nigra (47.3 % for ages 16–30 years). Sex hormones, especially those of pregnancy, are felt to promote the appearance of this line [24].

Periocular hyperpigmentation is observable in all races and is a combination of (1) more prominent vasculature under thin skin (especially with dermatitis present, i.e., the allergic shiner); (2) friction-induced pigmentary alteration; (3) hereditary hyperpigmentation and (4) external agents (e.g., ocular hypotensive agents usually noted in older adults). Coloration in Black patients is usually brownish with accompanying Dennie Morgan fold and surface xerosis being quite common.

Conclusions

Pigmentary variants are a normal part of cutaneous development in children of color. Recognition of the normal variant, while being mindful of potential systemic associations, allows the practitioner to counsel parents and provide reassurance and anticipatory guidance.

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Hypopigmenting Disorders

5

Joni M. Mazza, Candrice Heath, and Nanette B. Silverberg

Abstract

Loss of pigment, whether hypopigmentation, depigmentation, or dyspigmentation, is a common complaint in pediatric patients of color. Childhood loss of pigment can be divided into localized or generalized variants, congenital (under the age of 2 years at onset) or acquired, and by etiology. The following chapter identifies strategies to identify causes of pigment loss in children and reviews specific diagnoses commonly noted and pertinent to or with nuances in children of color worldwide.

Keywords

Loss of pigment • Hypopigmentation • Depigmentation • Dyspigmentation • Localized variants • Generalized variants • Congenital • Etiology

Epidemiology

- **Hypopigmentation is found commonly in pediatric dermatology practice with 4 % of pediatric dermatology cases presenting for hypopigmentation** [1]
- **0.5–2 % of the population worldwide has vitiligo**

Pathophysiology

Pigmentation begins in utero in the first trimester with the development of the neural tube and the neuroectoderm which gives rise to melanocytes. Migration of melanocytes in the first 12 weeks of gestation produces the segmental distribution termed the lines of Blaschko (Fig. 5.1), embryonic lines of growth which can be uniquely or distinctly pigmented, and the progress of pigmentation from back to midline and from proximal to distal extremities produces unique appearance of pigmentation in conditions such as piebaldism [2]. Other forms of pigmentary loss such as ash leaf macules in tuberous sclerosis begin later in utero or postnatally with the reduction in pigment production and/or transfer from melanocytes to the surrounding keratinocytes. Mutations in growth or tumor promoter genes can enhance the development of such abnormalities. Similar but generalized mutation in pigment genes will result in oculocutaneous albinism. Pigmentation is rarely complete at birth and often continues to evolve until the age of 2 years in children of color or beyond, resulting in sometimes delayed appearance of birthmarks of hypopigmentation or depigmentation. Acquired loss of pigment in later childhood can develop due to systemic therapies, postinflammatory pigmentary alteration (Fig. 5.1), after inflammatory conditions including seborrheic and atopic dermatitis, contact allergy, or leukoderma or autoimmune loss of pigmentation as noted in vitiligo or discoid lupus. Two studies in children of color, one Asian and one Indian, estimated that 3.28 per 1,000 or about 4 % of children in a dermatology clinic setting have hypopigmentation [1, 3]. Hypopigmentation and depigmentation are the outcomes of many disease processes in childhood ranging from congenital reduction or absence in pigmentation either localized or generalized to inflammation (e.g., atopic dermatitis, pityriasis alba) to autoimmune assault on melanocytes (e.g., vitiligo) [1–5].

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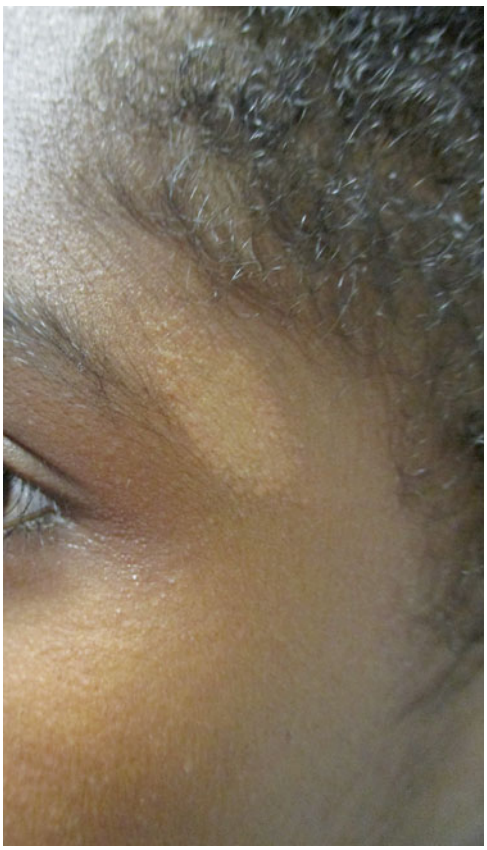

Fig. 5.1 Facial postinflammatory hypopigmentation due to prior atopic dermatitis lesions

Table 5.1 demonstrates a broad overview of loss of pigmentation in children, reviewing patterns of information and techniques to enhance diagnostic accuracy [1–8].

Tey recently described a basic paradigm to help diagnose hypopigmentation of childhood [6]. The classification developed is based on age at diagnosis, with division as "early" onset by 2 years of age vs. "late" onset age two or older. Further division by localized vs. generalized illness helps to discern diagnosis. The paradigm has one caveat: many congenital lesions have late expression, particularly in light-skinned children (e.g., nevus depigmentosus and pigmentary mosaicism). Furthermore there are rare situations where autoimmune or autoinflammatory diseases are congenital or extremely early in onset. Finally, most children of Black/African descent will develop hypopigmentation in response to seborrheic and/or atopic dermatitis (Fig. 5.1). Therefore we advocate a ten-step approach to evaluation of hypopigmentation in children summarized in Table 5.2.

Diagnoses

Review of every cause of hypopigmentation is not possible in this chapter. Focus on the most common causes of hypopigmentation is given with specific review by diagnosis (Table 5.1).

Nevus Depigmentosus

Epidemiology

- **0.4 % of Asian children are born with nevus depigmentosus** [3]**.**
- **34.2 % of cases are present at birth and most are present by age 3 years** [1].
- **Nevus depigmentosus is common in Hispanic children** [11]**.**
- **10.18 % of children seen for hypopigmentation in an Indian clinic were seen for nevus depigmentosus** [2]**.**
- **Multiple areas of pigmentary loss are uncommon and require careful evaluation for associated genetic syndromes.**

Post-zygotic alterations in pigment genes occur and can generate localized ovoid areas of hypopigmentation termed nevus depigmentosus. Single areas of pigment loss, similar in shape to a café au lait spot, are not uncommon in children of color, especially Hispanic children; however, multiple areas of pigmentary alteration are uncommon and require genetic work-up for genetic and/or chromosomal abnormalities and conditions such as tuberous sclerosis (ash leaf macules, confetti, and thumbprint-like hypopigmentation) [1, 9, 10]. 34.2 % of lesions are seen at birth and most lesions are noted by 3 years of age [1].

Clinical Presentation

- **Nevus depigmentosus is a localized hypopigmentation usually on the trunk or limbs that does not enhance on Wood's lamp examination.**
- **Lesions appear anytime from birth to age 2 years and may not become prominent until pigmentary development obviates the lesions.**

Nevus depigmentosum is a localized ovoid area of hypopigmentation that is non-enhancing with Wood's lamp (Fig. 5.2). Lesional appearance may be noted at birth or as late as age 3 years due to delayed pigmentary development. Hypopigmentation of the overlying hairs, the adjacent iris, and the mucosa can accompany a nevus depigmentosus [11]. Lesions are most commonly noted on the trunk, followed by the extremities. Wood's lamp examination can be used to identify early or subclinical lesions. The mexameter can be used to differentiate the nevus depigmentosus from vitiligo, by relative melanin index [12]. Similarly, in vivo confocal reflectance microscopy can be used to differentiate these lesions from vitiligo [13]. Differentiation from the ash leaf macules of tuberous sclerosis can be difficult and requires a high level of vigilance in screening for the stigmata of tuberous sclerosis. Biopsy shows normal number of melanocytes and reduced pigmentation of the epidermis with clumped melanosomes [5, 14].

Table 5.1 Diagnosis of hypopigmentation reviewed in this chapter

Type of hypopigmentation	History	Wood's lamp	Morphology/distribution	Dermoscopy	Biopsy	Further testing
Pigmentary mosaicism	Birth to 2 years	Equivocal	Linear in the lines of Blaschko; Multiple Lesions can signal hypomelanosis of Ito or genetic abnormalities	NC	Only for fibroblast culture and genetic testing	Screening for other systems affected, e.g., neurological alterations can aid in long-term care
Incontinentia pigmenti, 4th stage	Few weeks of life to mid-childhood; follows prior vesiculation, verrucous changes, or hyperpigmentation in the same distribution	Negative	Linear lesions in the lines of Blaschko	NC	Would be beneficial only in the vesicular or verrucous stage	Genetic testing and evaluation of family member
Menkes kinky hair carrier	Congenital through adulthood	Negative	Linear along broad lines of Blaschko	NC	NC	Genetic testing and evaluation of family member
Nevus depigmentosus	Birth through age 2 years	Negative	Annular area of partial pigment loss	NC	Genetic alterations could be detectable through culture of cells in this area and normal areas of pigmentation	Mexameter can differentiate from vitiligo Not necessary unless morphology is more consistent with ash leaf macules of tuberous sclerosis
Morphea	Childhood or adolescent acute onset; pruritus, burning, or pain can be associated; linear lesions (segmental form) can be noted and are associated with limb movement limitation and intracranial problems	Positive in some cases	Annular violaceous bound down plaques over the trunk or extremities	Vascular ectasia, atrophic epidermis might be noted	Biopsy would confirm morphea diagnosis	Not necessary unless linear lesions are noted over the head or neck
Lichen striatus	Onset in Spring, Summer, or fall abrupt and progressive distally to proximally along the extremities or on the face	Negative	Linear grouped small erythematous to flesh-colored papules resolving with hypopigmentation along the lines of Blaschko	Shows vascular ectasia and hyperkeratosis	Biopsy can demonstrate ball and claw lymphocytic clusters in the dermis	None needed
Postinflammatory pigmentary alteration	Any age, following the occurrence of cutaneous inflammation	Negative	Morphology consistent with previous insult	NC	Biopsy demonstrates presence of melanocytes	None needed
Waardenburg's syndrome	Congenital onset	NC	Hypopigmentation of the anterior shins with islands of repigmentation; typical clinical appearance, e.g., heterochromic irides, dystopia canthorum	NC	Biopsy may demonstrate absence of melanocytes	Genetic testing/counseling; Hearing screen; Check for signs of Hirschsprung's disease (rectal exam)
Piebaldism	Congenital onset	NC	White forelock Irregular white patches on face, trunk, and extremities often symmetrically distributed	NC	Biopsy may demonstrate absence of melanocytes	Genetic testing, family history

(continued)

Table 5.1 (continued)

Type of hypopigmentation	History	Wood's lamp	Morphology/distribution	Dermoscopy	Biopsy	Further testing
Mycosis fungoides	School-aged to adolescents	Positive in hypopigmented variant	Trunk, buttocks, and proximal extremities symmetric hypopigmented plaques with fine hyperkeratosis	Fine hyperkeratosis; vascular ectasia mild	Atypical lymphocytes; T-cell gene rearrangements	Good long-term prognosis
Nutritional Deficiencies – Kwashiorkor – Fad diets/food avoidance – Eating disorders – Gastrointestinal disease (IBD, pancreatic insufficiency, gastric bypass surgery) – Vitamin B12 deficiency – Vitamin D deficiency – Selenium deficiency – Homocysteinuria	Any aged child	Negative	Generalized hypopigmentation; hyperkeratosis; central enhancement	NC	May depend on the deficiency; often with pallor and ballooning of upper epidermis	Associated with malnutrition and gastric bypass procedures in adolescents. Type of cutaneous alteration depends on specific nutritional deficiency
Vitiligo	Onset in Spring of progressive pigment loss	Positive for highlighting	Hypopigmentation with good demarcation anywhere on the body, especially periorificial and intertriginous or over the joints of the extremities	NC	Biopsy would confirm the absence of melanocytes and potentially demonstrate lymphocytic infiltration at the active border	Mexameter can differentiate from nevus depigmentosus Thyroid tests and vitamin D levels are monitored standardly, but screening for other autoimmune illnesses can be performed on a case-by-case level
Oculocutaneous albinism	At birth	Negative	Generalized Hypopigmentation with or without pigmentary loss of the eye and/or hair	NC	Biopsy would confirm presence of melanocytes	Genetic testing and family history/screening may reveal the type associated with pigment loss
Tuberous sclerosis	At birth	Negative or equivocal	Hypopigmentation in format of thumbprints, confetti-like macules, and/or ash leaf macules; Later in childhood adenoma sebaceum, shagreen patch, and/or Koenen's tumor	NC	Biopsy pattern is in the differential of normal; however less melanin would be noted with special stains if compared to normal skin	Annual skin examination. Genetic screen, MRI of the head, neurologic evaluation, cardiac evaluation, nephrology evaluation, and developmental evaluation may all be appropriate in these patients.

NC non-contributory

Table 5.2 Ten-step approach to the diagnosis of hypopigmentation in childhood

Step 1: History
Age of onset
Presence of pigmentary loss in the hair or eyes
Review of past medical history including structural anomalies, intellectual impairments or learning disabilities, prior dermatitis, systemic illness (e.g., lupus erythematosus), drug exposures (e.g., hydroxychloroquine, antibiotics)
Personal/family history of seizures, autoimmunity, melanoma, atopy, and hypopigmentation
Step 2: Examination with and without Wood's lamp
Examine the patient in good lighting without a spotlight or halogen light for the skin, mucosa, hair, and eyes
Review of the skin for other skin findings consistent with diagnoses such as angiofibromas of the face, Koenen's tumors, or fibrous forehead plaque in tuberous sclerosis
Highlighting with Wood's lamp is seen in vitiligo, but may be noted in other conditions[a]
Step 3: Identification of lesion morphology
Confetti-like
Ovoid or annular
Over the joints or in the flexures
Placement along Langer's lines
Placement along the lines of Blaschko
Step 4: Identification of lesional distribution
Site
Localized vs. generalized
Unilateral vs. bilateral
Flexural vs. extensor locations
Linear/Blaschkoid
Presence of Koebner phenomenon
Number of lesions
Step 5: Identification of lesion thickness
Check for sclerotic changes or atrophy
Identify subtle hyperkeratosis suggesting plaques
Step 6: Usage of dermoscopy where needed to identify
Dermal alterations
Dilated blood vessels
Subtle thinning
Underlying pattern of pigmentation or vasculature (e.g., amelanotic melanoma)
Hyperkeratosis
Poliosis in vitiligo
Step 7: How to identify suspicious lesions that require biopsy
Buttock, periorificial, atrophic or for suspicion of malignancy or poor response to therapeutic trials (see Step 9)
Step 8: Further ancillary testing
Infectious testing: KOH, fungal culture
Karyotyping/genetic evaluation/genetic testing
Biopsy for fibroblast testing
Other referrals: e.g., neurology, ophthalmology
Step 9: Using treatment trials to identify subtle diseases
Possible treatment trial of topical mid-potency corticosteroids or tacrolimus
Step 10: Using suspected diagnosis to determine which blood tests to draw

[a]Silverberg JI, Silverberg NB. False "highlighting" with Wood's lamp. Pediatr Dermatol. 2012. doi:10.1111/j.1525-1470.2012.01787.x [Epub ahead of print]

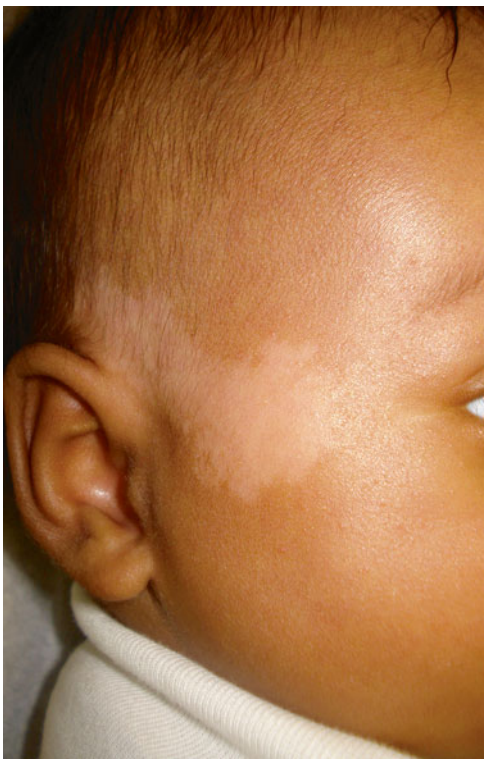

Fig. 5.2 Nevus depigmentosus on the face. This linear lesion was noted at birth. (From the Silverberg NB. Atlas of Pediatric Cutaneous Biodiversity. Spriner 2012, with permission)

Treatment

- **No treatment exists to remove these lesions other than surgery.**
- **Excimer light sources can temporarily tan lesions to make them less obvious.**
- **>Usage of grafts of pigmented skin or melanocytes can aid in lesional clearance.**

No current therapy for permanent removal, other than surgery, exists. Suction blister grafts and melanocyte keratinocyte grafts have been described to help clear lesions [15, 16]. Excimer laser has been described to reduce the prominence of these lesions [17]. A treatment trial with excimer laser can produce alterations on mexameter that differentiate such lesions from vitiligo. Pigmentary differences may become less marked with time in some children and disappearance can occur [18].

Menkes Kinky Hair Carrier

Epidemiology

- **Menkes kinky hair disease is a rare X-linked recessive defect in copper transport gene ATP7A associated with generalized hypopigmentation and neurologic degeneration** [19]

Clinical Presentation

- **Female carriers, due to random X inactivation, can present with localized or flag-like areas of hypopigmentation and variable neurologic defects** [20].

Treatment

- **No treatment exists for the therapy of the carrier state of Menkes disease.**
- **Prenatal diagnosis can be performed to prevent transmission of the gene when the mutation has been identified in the ATPA7 gene** [21].

Lichen Striatus

Epidemiology

- **Lichen striatus is a common, self-limited condition of childhood**

Lichen striatus is a common, self-limited condition of childhood seen in children of all ages and ethnicities and occurring year round. In a survey of 113 Indian children seen for hypopigmentation, 2 children had lichen striatus [1].

Clinical Presentation

- **Lichen striatus is typified by two phases of disease, a papular/eczematous phase** [22] **with a spreading, erythematous to flesh-colored plaque occurring along the lines of Blaschko**
- **A second phase characterized by prolonged postinflammatory hypopigmentation in children of color is noted upon clearance of the first stage**
- **Lesions are most common on the lower extremities**

Lichen striatus can be seen in children of all ages after infancy and follows a classical clinical course beginning with raised papular lesions that are erythematous to flesh colored along the lines of Blaschko, starting usually distally and progressing proximally along the lower extremity. It is usual for only one segment to be involved, but multiple segment involvement can occur [23–25]. Involvement of the nail with a non-scarring, self-limited dystrophy can be noted [26]. No seasonality is noted in larger studies. Upon resolution of the first phase, which usually takes 6 months but can rarely persist for 3–4 years, hypopigmentation will be noted in most children of Fitzpatrick types IV or higher (Fig. 5.4), with erythema as a sequela in some Asian children. Facial lichen striatus may resolve more rapidly according to one inner city study from the United States [27]. One case has been reported after allogeneic bone marrow transplant [28].

Treatment

- **Natural clearance is expected without scarring; therefore, therapy is not required.**
- **Therapies can be used to reduce pruritus or erythema or for cosmesis.**

While natural clearance is expected in most cases, in those individuals with symptoms or prominent lesions, topical pimecrolimus, tacrolimus [29], or retinoids with topical cortisteroids can be used to improve lesional appearance. Photodynamic therapy has been described as well [30, 31].

Pigmentary Mosaicism/Hypomelanosis of Ito

Epidemiology

- **Linear pigmentation along these embryological lines is termed pigmentary mosaicism**
- **When associated with structural or developmental anomalies, pigmentary mosaicism is termed hypomelanosis of Ito**.

The incidence of pigmentary mosaicism is unknown, but it is not rare, while hypomelanosis of Ito is uncommon, occurring in only 20–30 % of individuals with pigmentary mosaicism. There is no race or ethnicity more likely to be affected; however, due to lyonization, females may be more likely to manifest pigmentary mosaicism (Fig. 5.3).

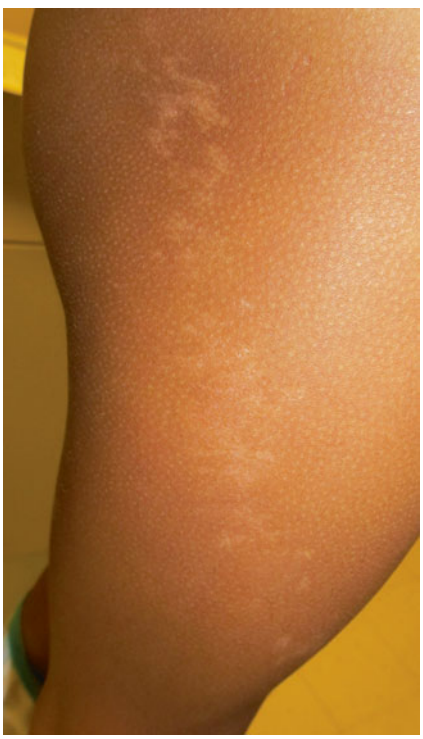

Fig. 5.3 Linear hypopigmentation after flattening of the papular phase of lichen striatus

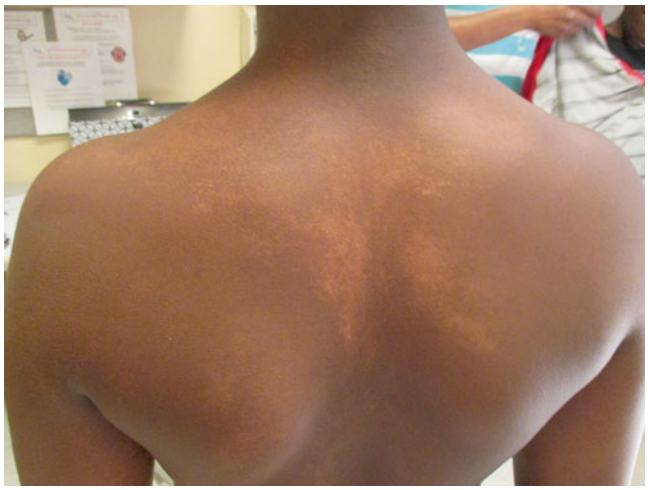

Fig. 5.4 Linear Hypopigmentation in a patten consistent with pigmentary mosaicism

Clinical Presentation

- **Hypopigmentation along the lines of Blaschko that is Wood's lamp negative or equivocal**
- **Multiple lesions, in association with structural and/or developmental anomalies, are termed hypomelanosis of Ito**

Pigmentary mosaicism usually appears at birth in darkly pigmented children, such as Indian or African-American children, or sometime in the first 2 years of life in Hispanic or Asian children. Mosaicism can be accompanied by hypertrichosis or hypotrichosis (Fig. 5.4).

Treatment

No current therapies are available for this disorder; however, judicious clinical monitoring for structural anomalies is recommended

While pigmentary mosaicism cannot be reversed, clinical monitoring is required developmentally in growth, limb lengths, and/or physical or speech development. Cardiac development, brain structure, and ocular development should be monitored.

Incontinentia Pigmenti

Epidemiology

- **X-linked dominant disorder that is rare**

Incontinentia pigmenti (IP) is an X-linked dominant disorder that only rarely affects living male children. It results from mutations in the nuclear factor-KB (NEMO/IKBKG) [32].

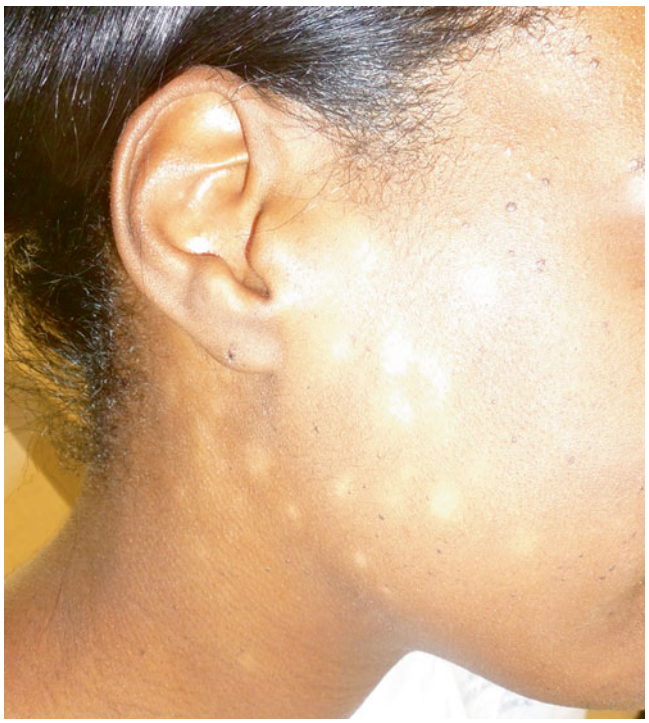

Fig. 5.5 Progressive macular hypomelanosis

Clinical Presentation

- **Four stages of development: vesicular, verrucous, hyperpigmentation, and hypopigmentation**
- **Dental, neurologic, and ocular anomalies can accompany the cutaneous features**

IP is apparent at birth or within a few weeks of birth. There are four well-recognized clinical stages of IP. Stage I is apparent at birth or up to 2 weeks of age and consists of linearly arranged vesicles, bullae, erythematous papules, pustules, and erythematous macules. Stage II of IP occurs between week 2 and week 6 of life consisting of linearly arranged verrucous papules. Hyperpigmentation along the lines of Blaschko characterize Stage III beginning at 3–6 months of age. Stage IV consisting of whorled hypopigmentation +/− atrophy, usually, is apparent by the second to third decade of life [32, 33].

Other clinical findings of IP may include pegged/conical teeth, scarring alopecia, dystrophic nails, ophthalmic abnormalities, seizures, mental retardation, and paralysis [32, 33]. (Also see pages 46-47).

Treatment

- **No current therapy exists for IP**

No current treatment exists for IP and treatment is not required clinically. Children who survive infancy have a good prognosis.

Nutritional Deficiencies Causing Hypopigmentation (Table 5.1)

Kwashiorkor

- **Protein-energy malnutrition (PEM) is the most common cause of nutritional deficiency worldwide. The two main forms are marasmus and kwashiorkor.**
- **Kwashiokor is defined as total body weight of 60–80% that expected for age and height with either edema and/or hypoalbuminemia.**

Kwashiorkor is due to insufficient protein intake, despite sufficient caloric intake, and is often seen in children with diets consisting entirely of rice or rice-based beverages. The children often develop failure to thrive, edema, and moon facies, as well as, marked muscle atrophy, hepatomegaly, and a distended abdomen with dilated intestinal loops. Frequent superimposed bacterial and fungal infections often complicate this condition. While PEM is rarely seen in developed countries, Lui et al. reported 12 cases of kwashiorkor diagnosed in the US in children without chronic medical illness. Six of the twelve cases were the result of poor nutritional education, fad diets, presumed food allergy and/or specific food avoidance.

Cutaneous manifestations include generalized hypopigmentation, dyschromia, pallor and xerosis. In mild cases, a superficial desquamation resembling flaking paint ("enamel paint spots") can be seen, while in more severe cases, confluent areas of eroded skin can occur. The hair in these patients can become thin, dry and abnormally pigmented, with a reddish tinge or occasionally even grey/white. The hair can also develop bands of light and dark colors, referred to as a "flag sign" which represents alternating periods of malnutrition and improvement of nutritional status. Clinical diagnosis should be confirmed with more objective markers including: easily detached hair, edema, skin fissures, faulty wound healing and skin anergy, as well as, albumin < 2.8 g/dl, transferrin < 150 mg/dl or total iron binding capacity < 200mcg/dl. Leukopenia can also be seen due to decreased cellular immunity.

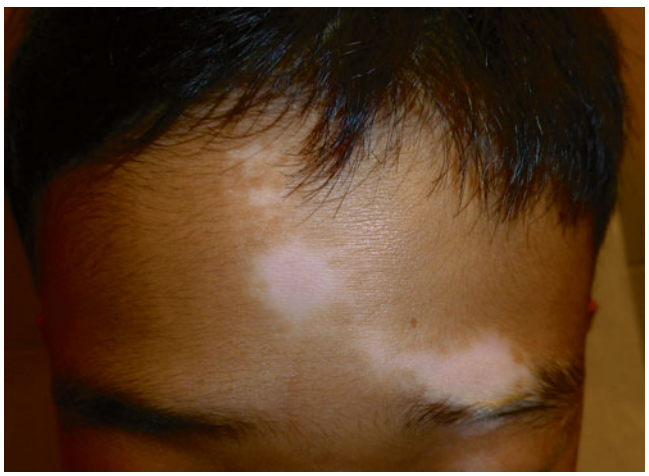

Fig. 5.6 Segmental vitiligo of the forehead

Fad diets, restrictive diets and eating disorders can also result in malnutrition and ultimately kwashiorkor. As in classic cases of kwashiorkor as described above, protein-energy malnutrition from diets can lead to similar cutaneous findings, such as xerosis and pigmentary changes of the skin and hair, and may even be the first appreciable signs of an eating disorder. A 2009 report described a 28 year old woman who presented for evaluation of scaly skin rash and lightening of hair color from brown to blond over the course of 4 years. After an extensive GI evaluation was performed, the patient was ultimately found to have combined vitamin and mineral deficiencies as well as kwashiorkor in the setting of anorexia nervosa and alcohol abuse.

Chronic malabsorptive states, such as those secondary to inflammatory bowel disease, celiac disease, pancreatic insufficiency and post GI surgery, can all lead to nutritional deficiencies. Protein-energy malnutrition has been reported in each of these settings resulting in kwashiorkor with associated findings of xerosis and hypopigmentation. Kwashiokor has been reported in the setting of infantile Crohn's disease with reversal of symptoms noted 2 weeks after treatment with prednisolone, azathioprine and nutritional supplementation. A 2011 case report of a Type 4/5 dark skinned patient with Kwashiokor secondary to a Whipple procedure used to treat chronic pancreatitis with pseudotumor at the head of the pancreas, demonstrated marked hypopigmentation of the skin and hair as well as ichthyosiform, xerotic skin. The patient was treated with a combination of nutritional support (hypercaloric oral diet, hyperproteic and with medium-chain triglycerides), vitamin supplements, oligoelements and oral replacement of pancreatic enzymes and within 3 months his pigmentation had returned to essentially normal.

Treatment

Treatment must be undertaken with caution, with a focus on correcting electrolyte abnormalities and treating infection. Malnutrition must be corrected with both balanced nutrition and increased caloric intake. Emollients can be used on the skin and cutaneous lesions tend to improve with treatment of the malnutrition.

Vitamin/Mineral/Enzyme Deficiencies

Vitmain deficiencies have also been implicated in hypopigmentation. A case of hyperpigmented macules on the body,

longitundal hyperpigmented streaking on the nails and gingiva hyperpigmentation along with diffuse whitening of the hair in a 55 year old female was seen in the setting of Vitamin B12 deficiency. These pigmentary alterations were reversed in 2-3 months, with correction of her Vitamin B12 deficiency. Additionally, Extensive confetti like vitiligo has been described in association with extremely deficient levels of vitamin D.

Selenium deficiency, though rare, can be seen in cases of total parenteral nutrition (TPN), chronic bowel disease and following gastric bypass surgery. It can also be seen in people who survive on diets derived entirely from selenium deficient soil.

Postinflammatory Pigmentary Alteration

Epidemiology

- **Postinflammatory pigmentary alteration is a leading chief complaint for patients of color.**
- **While the incidence is unknown in children, virtually all children of color will experience postinflammatory pigmentary alteration.**

Postinflammatory pigmentary alteration is a pigmentary alteration of the skin that is seen in children of color from early infancy through adolescence. Causes of dyspigmentation include primarily hypopigmentation early on, with the leading insult being seborrheic dermatitis and atopic dermatitis (Fig. 5.1). With increasing age, hyperpigmentation is a common postinflammatory change, seen after bug bites, acne, and eczema lesional clearance.

Clinical Presentation

- **Discrete, well-demarcated areas of pigmentary alteration, either hypopigmentation or hyperpigmentation, are noted.**
- **Pigmentary alterations should be self-limited, but cantake years to resolve in darkly pigmented individuals.**

Treatment

- **Resolution without therapy is expected in most cases**
- **Therapies include treatment of the underlying cause and sun protection**
- **Bleaching, chemical peels, and fraxel laser can be used in older patients to speed resolution.**

Waardenburg's Syndrome

Epidemiology

- **Waardenburg's Syndrome is inherited via autosomal dominant inheritance and is characterized by four subtypes.**

Waardenburg's Syndrome types I and III are due to mutations in the PAX3 transcription factor gene. The PAX transcription factor is a key component in neural crest differentiation, melanoblast activation, melanoblast migration, and structures involving the facial bone, facial cartilage, and inner ear. Waardenburg's Syndrome type II is due to a mutated melanocyte transcription factor, MITF gene. Type IV is due to mutations in SOX10 transcription factor, endothelin-3 gene, and endothelin receptor which all affect neural crest development [32].

Clinical Presentation

The main skin finding in Waardenburg's Syndrome is depigmented patches with overlying hyperpigmented patches, i.e., islands of repigmentation. Other clinical features may include a white forelock, synophrys, dental caries, broad nasal root, dystopia canthorum (not in type II), heterochromia iridum, congenital sensorineural hearing loss (most common in type II), and Hirschsprung's disease (type IV) [32, 34, 35]. Cleft lip and palate may be seen in type I and musculoskeletal defects of the upper limb and pectoral muscles may be seen in type III [32].

Treatment

- **There is no cure for Waardenburg's Syndrome.**
- **Patients should be evaluated by specialists who can address the known potential characteristics of the syndrome.**
- **Pregnant mothers who have a family history of Waardenberg's syndrome should take folic acid supplementation due to reported familial cases of neural tube defects.**

Waardenburg's syndrome patients should be screened by specialists for the known features of the syndrome. Hearing screen, rectal examination and genetic testing/counseling are reasonable screening tests for Waardenburg's syndrome patients. There have been reports of neural tube defects in Waardenberg's syndrome patients. Folic acid supplementation, though recommended for all women of child bearing age, may be of particular importance in this at risk group [36].

Piebaldism

Epidemiology

- **Piebaldism is a rare autosomal dominant disorder caused by mutation in the KIT proto-oncogene.**
- **Piebaldism is caused by abnormal melanocyte migration and melanosome transfer, resulting in white forelock and depigmentation over the abdomen and circumferentially on the extremities.**

Piebaldism is a rare autosomal dominant disorder, characterized by congenital absence of melanocytes due to abnormal melanocyte migration and melanosome transfer [1], resulting in a classic white forelock and/or multiple, symmetric depigmented patches of skin. The disorder results from mutations in the KIT proto-oncogene, which encodes a cell surface, tyrosine kinase receptor for an embryonic growth factor, steel factor. The KIT gene is involved in melanoblast proliferation, migration, and differentiation [37]. A review of the literature in 2001 demonstrated 14 point mutations, 9 deletions, 2 nucleotide splice mutations, and 3 insertions of the KIT gene that resulted in the phenotypic piebaldism. Varying degrees of severity are reported, based on type of mutation, with dominant negative missense mutations resulting in the most severe phenotypes. Association with acquired vitiliginous pigmentation has been described [37]. Overall prevalence of the condition is unknown. Worldwide incidence does not seem to vary, and reports in all races and ethnicities have appeared in the literature (Fig. 5.7).

Clinical Presentation

- **Congenital depigmentation with the combination of white forelock and depigmented patches over the central abdomen and circumferentially around the extremities.**

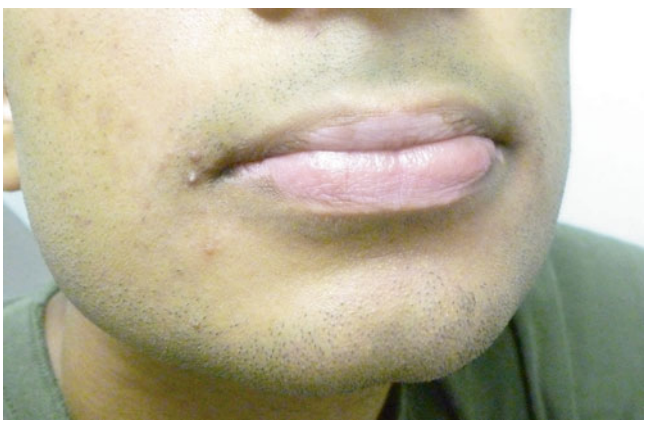

Fig. 5.7 Extension of perioral vitligo onto the face in a patient with lip and mucosal depigmentation of non-segmental vitiligo

- **Islands of repigmentation and vitiligo have both been associated with piebaldism.**

Skin lesions are present at birth or when hair color first becomes apparent. 80–90 % of patients with this condition will have a white forelock, occasionally in a triangular shape. Eyebrow and eyelash hair may also be affected. Irregularly shaped white patches on the face, chest, abdomen, and extremities are often symmetrically distributed, with islands of hyperpigmentation either within or at the border of lesions. While generally the depigmentation is permanent, regression has been described [38]. In patients of color, depigmentation is more notable at birth and is very prominent early on. Confusion with vitiligo is not uncommon.

Occasionally, piebaldism is seen in association with other conditions, such as Hirschprung disease, neurofibromatosis type I, congenital dyserythropoietic anemia type II, Diamond-Blackfan anemia, Grover disease, or transient acantholytic disease [39].

Treatment

- **Piebald absence of pigmentation generally requires no care but can be treated with cosmetic camouflage or graft procedures.**

While piebaldism is a benign clinical condition, it is not without potential psychosocial impact, particularly in patients with skin of color. Unfortunately treatment can be quite challenging, as these lesions are typically unresponsive to conventional medical or light therapies. Camouflaging makeup or topical tanners containing dihydroxyacetone can be tried. Success has been reported in 12 adult patients with the use of dermabrasion and split thickness skin grafts followed by minigrafting, and subsequent irradiation with UVA [40]. Autologous punch grafting and erbium YAG followed by autologous cultured epidermis have also been utilized with success [41, 42].

PLEVA/MF (See Chapter 3)

Oculocutaneous Albinism

Epidemiology

- **Albinism comprises a group of inherited disorders characterized by a congenital reduction or absence of melanin.**
- **There are four subtypes of oculocutaneous albinism 1–4, with variable loss of pigment and associated findings.**
- **Some subtypes are more common in patients of color.**

Albinism comprises a group of inherited disorders characterized by a congenital reduction or absence of melanin. While phenotypically there is variability among patients, the

condition is generally classified into two groups: oculocutaneous albinism (OCA) and ocular albinism (OA). In OCA, the reduction or absence of melanin presents phenotypically as hypopigmentation or depigmentation of the skin, hair, and eyes. In the United States, it is estimated that 1 in 17,000 people have albinism. Males and females can both be affected, as most types of the disease are autosomal recessive, though OA1, which is X-linked recessive, can only present in males. This condition is seen in all ethnicities.

OCA was previously defined as being tyrosinase negative or tyrosinase positive; however in 2009, the diagnosis was reclassified based on genetic mutation and divided into four major subtypes: OCA1–OCA4 (see also Chapter 3).

Clinical Presentation

- **Absence or reduction in pigmentation will be noted in the skin, hair, and eyes from infancy.**
- **Children will be prone to sun damage and phototoxic reactions due to reduced melanization.**

OCA1 is due to mutations in the tyrosinase gene located on chromosome 11. Based on type of mutation, this condition can be further subdivided into OCA1A and OCA1B. OCA1A, the classic tyrosine-negative albinism, is due to complete absence of tyrosinase and therefore the most severe phenotype of this disorder. These patients have striking hypopigmentation at birth with white hair, pale, translucent skin, and blue eyes. They have decreased visual acuity, increased incidence of photophobia and strabismus, and an increased risk of skin cancer. OCA1B (yellow mutant OCA, Amish albinism) is due to reduced tyrosinase activity. Degree of pigmentation can vary, and while these patients are typically hypopigmented at birth, with age they commonly develop yellow hair and darkening of the eyes.

OCA2 (tyrosinase-positive albinism), the most common form of the disease, particularly in African-American and African populations, is due to mutations in the P protein, located on chromosome 15. In Caucasians, this variant presents phenotypically with blond hair and blue-gray eyes, and pigmentation increases with age. In African-American and African patients, this type classically presents with white skin, yellow hair, and blue-gray irides, and darkening does not commonly occur with age.

OCA3, previously termed red or rufous OCA, is due to mutations of the tyrosine-related protein 1 (TYRP1) gene, which acts as a regulatory protein in the production of eumelanin. Mostly reported in Africa and New Guinea, OCA3 manifests as light brown or reddish brown skin and hair color, and ocular involvement is not typically a feature.

OCA4 is caused by a mutation in the membrane-associated transporter protein (SLC45A2) and can only be distinguished from OCA2 by genetic testing [43].

Phototoxic reactions are more common in children with OCA and skin cancers especially squamous cell carcinomas, basal cell carcinomas, and amelanotic melanomas can be noted [44].

Treatment

- **Photoprotection and continuous skin monitoring are required**

There is no cure for this condition and most patients have a normal life span and average intelligence with no developmental delay. Sun protection is critical in these patients to prevent the development of skin cancers. Additionally, prevention of vision loss and management of ocular symptoms through the use of vision aids and tinted glasses to prevent photophobia are critical.

Experimental

Recently, the use of nitisinone has been reported as a potential treatment option [45]. Currently this drug, which increases plasma tyrosine levels, is FDA approved for treating hereditary tyrosinemia type 1. In 2011, it was shown in mouse models of OCA-1b to increase plasma tyrosine levels and subsequently increase eye and hair pigmentation, and therefore many represent a potential future treatment option [46]. Psychosocial impact must also be addressed in these patients, particularly in cultures that continue to stigmatize this condition [47] (Table 5.3).

Hermansky–Pudlak Syndrome

Hermansky–Pudlak syndrome (HPS) is a rare autosomal dominant condition that can be seen in patients with OCA. While the disorder can be quite heterogeneous, with nine subtypes, it is characterized by "tyrosine-positive" OCA, a platelet storage pool defect leading to bleeding diathesis and systemic manifestation due to lysosomal storage defects. Clinically, patients have a phenotype similar to that of OCA2. A ceroid-like substance accumulates in the lysosomes of various organs in patients with HPS. This can lead to sequelae such as pulmonary fibrosis, renal failure, and granulomatous colitis. Abnormal platelet function is common in this condition.

The condition is frequently seen in patients of Puerto Rican descent. Five out of six patients with OCA have HPS type 1 and 1 out of 21 people in the northwest quadrant of Puerto Rico carry the gene for HPS type 1. Cases of HPS in US Hispanics not of Puerto Rican descent have also been reported [48].

Patients with the clinical phenotype suggestive of this disease should have microscopic evaluation of their platelets to

Table 5.3 Oculocutaneous albinism

	Gene	Incidence	Subtype	Clinical features
OCA1	TYR	1 in 40,000	OCA1a	No pigment Vision 20/200-20/400
			OCA1b	Some pigment
			– OCA1b TS	Temperature sensitive—tyrosinase can function in cooler temperatures
			– Albinism yellow mutant type	Seen in Amish; blond hair and increasing pigmentation during infancy
OCA2	OCA2 (formerly P gene)	1 in 36,000 in white Europeans 1 in 4,000 in some parts of Africa		More pigment and better vision than OCA1 African patients have yellow hair, pale skin, and blue-gray eyes
OCA3	TYRP1	More common in Africans	Previously called "rufous" or red OCA	Red hair and reddish brown skin Minimal to no visual disturbances
OCA4	MATP (SLC45A2)	Rare; has been described in Turkish, German, Japanese, and Korean patients		Phenotypically identical to OCA2 Visual acuity decreased, nystagmus

assess for absence of dense bodies. PT and PTT as well as the number of platelets are likely to be normal.

There is no cure for this disease and patients with HPS suffer high rates of morbidity and mortality. The average life span is 30–50 years and death typically results from complications of the disease such as pulmonary fibrosis or hemorrhage. Management of the condition is largely based on sun protection, vision correction, prevention of hemorrhage, and close medical monitoring for systemic disease.

Progressive Macular Hypomelanosis

Epidemiology

- **The term "progressive macular hypomelanosis" was first coined by Guillett in 1988 where it was described in skin of color patients of various ethnicities in the French West Indies [49]**
- **While the condition can be seen in all skin types, it is most commonly reported in darker skinned patients, particularly from tropical countries.**
- **PMH is more common in young women, but can be seen in men as well, and the natural progression is for spontaneous resolution by middle age**
- **Progressive macular hypomelanosis (PMH) is a relatively common skin condition that is often misdiagnosed as tinea versicolor or pityriasis alba.**
- **The condition is characterized by nummular, non-scaly, hypopigmented macules and patches on the trunk, generally centered around midline, but can extend to the extremities, face and neck (Fig. 5.5).**
- **Lesions are entirely asymptomatic.**

On histopathology, decreased pigment is noted in the epidermis overlying a normal dermis. Electron microscopy demonstrates a change in melanosome structure from large melanosomes in normal skin to smaller, aggregated melanosomes in the hypopigmented areas.

While the etiology remains entirely unknown, Westerhof et al. in 2004 proposed P. acnes as a causative agent in this condition, based on the presence of the bacteria in hair follicles examined under Wood's lamp in eight of nine patients and anaerobic culture of same [50, 51].

Treatment

- **The condition is difficult to treat and topical steroids, topical antifungals, topical antibiotics and benzoyl peroxides, oral tetracyclines, and NB-UVB and UVA have all been tried with variable results.**
- **A recent case report showed excellent results with isotretinoin. Additional studies with long-term follow-up are necessary [51].**

Vitiligo

Epidemiology

- **Vitiligo is a disorder of pigment loss that is believed to be autoimmune in most cases**
- **0.4–2 % of the worldwide population has Vitiligo**
- **Half of all vitiligo cases are believed to occur in childhood**

Vitiligo is an autoimmune form of pigment loss. Half of all cases occur in childhood [52]. 0.4–2 % of the worldwide population has vitiligo [53]. A recently published Chinese population based survey of over 17,000 people confirms that the prevalence is 0.56 %, with 0.1 % in 0–9-year-olds and 0.36 % in 10–19-year-olds [54]. Prevalence has been noted somewhat lower (0.18 %) in a population-based study of 2,194 Sinai

desert Egyptian children [55]. The prevalence of vitiligo in children in a Tanzanian clinic was 0.7 % [56]. Vitiligo in the first decade of life may occur somewhat more frequently in females in some studies [32, 57]. Although racial predilections are not known in vitiligo, association of the disease with tan/brown eyes suggests linkage to skin of color [58].

Onset of vitiligo in childhood varies around the world. In China, a study of 620 children showed an average age of 7.57 years. In a group of Indian children, average age of onset was 6.9 years, with slight female predominance [59]. Age of onset in a mixed adult and pediatric population in Saudi Arabia was 17.4 years, also with a slight female predominance [60]. In a Brazilian population, patients with segmental vitiligo had onset of vitiligo at 16 years, while the general vitiligo grouping had onset on average at 23.9 years [61]. Incidence in a consecutive series of 2,000 children in Jordan showed prevalence to be 0.45 % <1 year, 1 % aged 1–5 years, and 2.1 % aged 5–12 years [62]. In a cohort of Turkish children, average age of onset was 7.26 ± 4.43years [63].

Many genes have been linked to vitiligo in genome-wide association studies. These have included pigmentary genes, mutations in which contribute to the antigenicity of the melanocyte and the promotion of autoimmunity. These genes include tyrosinase (TYR), OCA2, the gene which is mutated in oculocutaneous albinism type 2, HERC2, and MC1R, the alpha melanocyte stimulating hormone receptor [37, 64]. Specific MHC loci have been linked to vitiligo as well especially the HLA-A*02:01 locus [20]. B- and T-cell alterations (CTLA4, BACH2, CD44, IKZF4, and LNK) [65, 66], as well as changes in the innate immune system (NLRP-1 and CASP-7) [67], have also been linked to vitiligo. These changes in the immune system have been reflected histologically by the detection of dendritic cells and mature T cells at the borders of new vitiliginous lesions and detection of anti-melanocyte circulating antibodies [68–71]. Promotion of pigment cell through reactive oxygen species generation has resulted in reporting of a variety of antioxidant vitamin regimens in Non-segmental vitiligo [72–75]. The final pathway of melanocyte destruction is apoptosis preceded by melanocytorrhagy, a poor cellular melanocyte attachment [76, 77].

Vitamin D deficiency (<15 ng/dL) has been linked to risk of polyautoimmunity in children aged 3 and over in the United States with vitiligo. Chinese patients with vitiligo have also been found to have high risk of vitamin D deficiency and an increasing risk of thyroid disease when deficient over insufficient. Specific vitamin D receptor genotypes have been linked to reduced risk of vitiligo in an Asian cohort [78]. Vitamin D insufficiency screening and supplementation is recommended accordingly [79–82].

Chemical triggers of leukoderma and/or vitiligo have been reported and contact with hair dyes containing para phenylenediamine and avoidance may aid in reduction of vitiligo risk on the head and neck [83].

Clinical Presentation

- **Vitiligo can be segmental (SV) or non-segmental (NSV), i.e., generalized.**
- **NSV presents with hypopigmented to depigmented patches in the periorificial and intertriginous areas and over the joints.**
- **In NSV, depigmentation can progress over time in the involved areas.**
- **SV usually follows the lines of Blaschko and has limited hypopigmentation spread within those segments.**

Vitiligo can be segmental (SV) or non-segmental (i.e., generalized) or may overlap these two variants (mixed type), rarely. Segmental vitiligo follows the lines of Blaschko and starts off with an early rapid phase followed by stabilization (Figure 5.6). SV is more common in childhood with 87 % of cases occurring by age 20 years [84]. Halo nevi and leukotrichia are initial clues of conversion from SV to mixed type [85]. NSV has a greater number of lesions, body surface area, and Koebner phenomenon [84]. Rare extension to complete pigment loss occurs in less than 1 % of patients [86, 87].

Vitiligo affects the skin with hypopigmentation over the joints, intertriginous and periorificial areas (Figure 5.7), and genitalia [88]. Vitiligo often presents in Spring and Summer in fair-skinned individuals and is more prominent and emotionally disturbing in darker patients, especially Black patients [89, 90].

Physical examination will show typical pattern of symmetric pigmentary loss that enhances with Wood's lamp [91]. Dermoscopy can be used to demonstrate poliosis, suggesting the loss of pigment reservoir and greater difficulty in repigmentation [92].

NSV is associated with personal and familial risk of autoimmune diseases, including thyroid disease with incidence of up to 26 % worldwide, requiring careful exploration. In survey of pediatric patients with vitiligo reported comorbidities were thyroid disease (5.4 %), rheumatoid arthritis (1.1 %), psoriasis (1.1 %), and alopecia areata (0.8 %). Prolonged disease was associated with greater risk of thyroid disease with Hashimoto's being twice as common as Grave's disease [93–96]. Outside the United States studies have linked vitiligo as well to Celiac disease, pemphigus vulgaris, and Addison's disease [97]. Polyautoimmunity can be part of Schmidt's syndrome or polyglandular autoimmune syndrome or rarely be seen in the setting of Schmidt's syndrome or Vogt–Koyanagi–Harada syndrome, which is a combination of autoimmune attack on multiple pigmented tissues including the eye, ear, meninges, and skin [98, 99].

Psychological impairments are noted in children with vitiligo including poor self-image, susceptibility to bullying, and specific deficits on children's dermatology quality of life index. One-third of children will experience pruritus and this correlates with susceptibility to bullying, as does facial

disease [100–102]. As many as 51.1 % of children will have notable psychological sequelae of vitiligo, especially with advancing age from childhood to teen years, and advancing surface area >25 %. Psychological intervention may be required to enhance self-image and socialization skills in teenagers, as well as to blunt disease progression [100, 103–106]. Skin cancer risk in adults with vitiligo is one-third that of their spouses; however, risk in childhood is unknown [107]. Rare reports of melanoma presence at vitiligo onset suggest that inquiry as to changing lesions is warranted in new onset vitiligo [108].

The differential diagnosis of vitiligo depends on the age of the patient. In early childhood, nevus depigmentosus, tuberous sclerosis, Piebaldism, and Waardenburg's should be considered. In later childhood and adolescence, postinflammatory pigmentary alterations after dermatitis, hypopigmented mycosis fungoides, and lichenoid dermatoses can be considered [6]. Biopsy can be performed to identify absence of melanocytes in cases that cannot be diagnosed clinically.

Laboratory studies are controversial in vitiligo and are likely not required in SV. In NSV or mixed vitiligo, the current data support periodic thyroid screening, blood count (anemia would reflect B12 deficiency and/or folate deficiency), and monitoring of vitamin D levels. In the setting of vitamin D levels below 15 ng/dL, searching for antinuclear antibody, pernicious anemia, diabetes, and rheumatoid arthritis may be needed, especially where photosensitivity and/or joint pain are noted. Celiac screen is warranted in the setting of abdominal cramping or other abdominal symptomatology [109].

Treatment

- **For SV, topical tacrolimus demonstrates benefit in repigmentation.**
- **NSV of childhood can be treated using calcineurin inhibitors (e.g., tacrolimus) for the face, eyelids, and sensitive areas (e.g., intertriginous locations).**
- **For NSV of the body and/or extremities, mid-potency topical corticosteroids can be used (e.g., mometasone) to enhance repigmentation.**
- **In extensive cases of NSV, narrowband UVB can be used to stabilize disease and effect repigmentation.**
- **Excimer laser can be performed in resistant skin lesions to enhance repigmentation, and is particularly useful within the first few months of onset of SV.**

The mainstay of therapy for vitiligo in childhood for 40 years had been topical class 2 corticosteroids and previously psoralens and UVA. A tremendous series of advances have occurred in the therapy of vitiligo since 2004, including the usage of topical calcineurin inhibitors, very helpful for facial lesions and recent onset disease, narrowband UVB with an improved safety profile over PUVA, topical calcipotriene, and excimer laser. Vitiligo therapy is especially important in individuals of color. In a recent survey of Saudi dermatologists, 76 % felt disease was not purely cosmetic [110].

Children with vitiligo need to be evaluated first for the presence of comorbid illnesses including vitamin deficiencies and secondary autoimmunity (e.g., autoimmune thyroid disease), the screening for which is reviewed in clinical presentation. Topical, oral, and phototherapeutic options need to be offered, along with psychological care and guidance on lifestyle.

Therapies can work via the rescue of damaged pigment cells from inflammatory destruction, clearance or reduction of inflammation, quenching of free radicals, promotion of repigmentation through the enhancement of migratory movement of melanocytes from follicles or borders of lesions, and transplantation or grafting of melanocytes from other cutaneous sources [111]. All topical therapies for vitiligo are off-label and not FDA approved, making for difficulty in obtaining health coverage of therapy. Therapies should be chosen based on location of disease, length of lesional presence, and response to prior therapy.

Tacrolimus is a calcineurin inhibitor originally described as a systemic medication for the prevention of graft rejection. Topical tacrolimus has been approved for the topical therapy of children aged 2 and over with atopic dermatitis previously unresponsive to topical corticosteroids. Tacrolimus is not atrophogenic and is suitable for application on the face, eyelids, intertriginous areas, and genitalia. Tacrolimus has been reported to be effective for the topical care of vitiligo in childhood and has been used for this indication for a decade [105, 112, 113]. Repigmentation is best over the head and neck, with enhanced results for patients of color (Fitzpatrick types III–IV), for facial segmental disease, and for recent onset lesions (<5 years) [114]. Acral lesions have a poor response to tacrolimus. Dosage chosen for tacrolimus therapy should follow pediatric dosing of atopic dermatitis, 0.03 % for 2–15 years and 0.1 % for children ages 16 or over and a minimum of 3-month trial should be given [92]. In a 2-month comparative trial of clobetasol propionate 0.05 % ointment and tacrolimus 0.1 % ointment are similarly efficacious in childhood facial vitiligo [115, 116]. A recent study comparing efficacy of tacrolimus in adults and children showed children have nine times the efficacy of adults with regard to excellent repigmentation [117]. Enhancement of results is noted with the addition of excimer laser; however given the black box warning for theoretical skin cancers with tacrolimus, this combination is controversial [118]. Other side effects with tacrolimus include acne and a burning stinging sensation [119].

Pimecrolimus is approved in the United States for the care of mild-to-moderate atopic dermatitis and can be used for vitiligo with similar locations of application to tacrolimus.

A randomized Turkish trial of pimecrolimus vs. mometasone cream showed 42 vs. 65 % repigmentation at 3 months with weak response on the body and hands [120]. Greater response is noted with preceding microdermabrasion in Egyptian children and with paired excimer laser therapy, the latter bearing a theoretical skin cancer risk [121, 122].

Topical corticosteroids, with or without topical calcipotriene can repigment vitiligo [116]. The Vitiligo European Task Force has recommended mometasone as a first-line agent for treatment of vitiligo on the body, and tacrolimus for facial vitiligo in childhood as a first-line agent [82]. Ongoing topical corticosteroids can cause cutaneous thinning, telangiectases, acneiform lesions, hypertrichosis, and potential inhibition of pigmentation. Glaucoma can occur with prolonged periocular usage. Topical tretinoin and calcipotriene can both be steroid sparing and reduce side effects [123–126]. Cyclic therapy of vitiligo using topical agents maximizes response to available products, since it is rare to achieve 100 % repigmentation with any one agent. Cycling can be done every 3–4 months on the head and neck and every 6–8 months on the body where greater time is required to achieve maximal response. The addition of phototherapy into the cycle can enhance response in extensive disease and excimer laser can be reserved for limited unresponsive disease [127].

Minipulses of oral betamethasone/dexamethasone have been described to stabilize and repigment vitiligo over a 2–4 month time period [128–130]. Psoralens and UVA were reported to produce 67 % repigmentation in 64 sessions for patients aged 14–32 years, but caused high risk of phototoxic reaction and is difficult for pediatric compliance due to need for prolonged eye protection and difficulty standing in a phototherapy booth for prolonged periods of time [131, 132]. Phototherapy using narrowband UVB has also been described to stabilize disease in 80 % of children in the Netherlands when administered twice weekly over a year's time period, with 53 % of patients achieving >75 % repigmentation. Narrowband UVB has largely replaced PUVA due to reduced risk of sunburn, lesser skin cancer risk in psoriatics, and lack of need for prolonged eye protection. Furthermore, PUVA was very unlikely to provide 50 % repigmentation as compared to clobetasol topically [133, 134]. Phototherapy is used for large surface area disease, advancing disease, and disease poorly responsive to topical therapy [134]. Narrowband UVB has been shown more effective in recent onset illness. Outcomes correlate to early response patterns, facial disease, and skin types 3–4. Therapy for more than 6 months without response would be indication for therapeutic discontinuation [135–137]. Tacrolimus topically can enhance response to narrowband UVB. Alternatively, topical corticosteroids can be used to enhance response to NB UVB [138, 139]. Therapy with a localized application of the 308 nm ultraviolet laser can enhance repigmentation in childhood without systemic exposure to narrowband UVB [140]. Excimer is particularly helpful within the first few months of SV onset, as demonstrated by a recent Korean study and would bear a lower risk of skin cancer [141].

For localized disease that has been depigmented for extended time periods without good response to therapy, grafting can be performed. Grafting brings in pieces of whole skin (e.g., punch or suction grafts) from areas of full pigmentation. Irregular texture or cobblestoning can occur, with potential for scarring or keloid formation in patients of color. Pediatric response is usually considered to be very good, but newer techniques like melanocyte suspension grafts require addition of growth factors and the long-term safety is unknown [142–145]. Repigmentation can be enhanced with narrowband UVB, excimer, or PUVA therapy [140, 146].

When standard methods fail or when an older adolescent's disease advances rapidly, depigmentation can be contemplated. In this situation, psychological screening is required to determine that the patient is psychologically able to handle color removal [104]. Depigmentation is usually performed using 20 % monobenzyl ether of hydroquinone which is no longer commercially produced in the United States [104]. Specialized makeup can be used to camouflage obvious lesions and help children avoid unwanted attention to their lesions [147].

Experimental Treatments and Ongoing Research

Afamelanotide, alpha melanocyte stimulating hormone analogue, is under testing, but preliminary results indicate rapid early repigmentation is noted when paired with narrowband UVB [148]. Broadband UVA is an emerging therapy that may give better results than narrowband UVB, but there is no good data in children and the treatment is not currently found in the United States [149]. A heat shock protein 70 analogue is under development in animal models [150].

Tuberous Sclerosis

Epidemiology

- **The birth incidence of tuberous sclerosis is believed to be 1 in 5,800 individuals** [151]**.**
- **Tuberous sclerosis is an autosomal dominant condition with variable but high penetrance of lesions** [152, 153]**.**
- **Tuberous sclerosis is caused in 75–90 % of cases by a mutation in either hamartin (TSC1) or tuberin (TSC2)** [154, 155]**.**

Tuberous sclerosis (TS) complex is a genetic disorder of skin lesions and multiple tumors, usually benign, in a variety of organ systems that can result in seizures, often intractable (infantile spasms), intellectual disability or autism, and a variable degree of organ dysfunction in virtually any organ of the body. TS can be seen in any race or ethnicity of patients

and affects males and females with the same frequency; however, pulmonary findings are more common in women. Everyone with TS will have manifestations whether in utero (cardiac rhabdomyomas), childhood, adolescence, or adulthood. Early identification can be performed clinically for affected family members of affected individuals, or may be done via screening for gene mutations when the family index case has had one identified [151–155].

Clinical

- **Tuberous sclerosis is a multisystem disorder that affects the skin, neurologic system, heart, mouth, eyes, kidneys, liver, and lungs.**
- **In 2012, the consensus criteria for tuberous sclerosis were modified to require two or more of 11 major criteria or one major and two or more of 6 minor criteria.**

The major criteria for TS are either confirmed pathogenetic germline mutation in TSC1 or TSC2 or clinical criteria. The clinical criteria include four cutaneous and seven extracutaneous findings. The most common early childhood cutaneous clinical finding, seen in >90 % of patients, and one of the major criteria for TS are hypomelanotic macules (≥3, 5 mm or more in size). In infants or individuals of light skin tone, Wood's lamp may be used to identify hypopigmentation that is not visible to the naked eye. Hypopigmented macules, sometimes termed ash leaf macules, are often the presenting sign of TS that prompts diagnostic work-up. Such evaluation is recommended in all family members of individuals with TS and in children with infantile seizures/spasms, suggestive of TS. In children with Fitzpatrick skin types 4–6, lesions may be notable at birth. The other major criteria involving the skin include angiofibromas (≥3) or fibrous cephalic plaque (previously termed fibrous forehead plaque), ungual fibromas (≥2), or the shagreen patch. Angiofibromas, seen in 75 % of TS patients, are flesh colored to erythematous papules noted perinasally and on the cheeks and begin to appear around preschool entry (ages 2–5 years) through adolescence, while the fibrous cephalic plaque, seen in 25 %, usually appears in adolescence any place on the head or scalp and is histologically similar to angiofibromas. Ungual fibromas may be trauma induced and become more frequent in adulthood, especially in the geriatric grouping. The shagreen patch (a form of connective tissue nevus) is a large flesh-colored to pink plaque with peau d'orange surface appearance on the lower back in children in early childhood. In children of Fitzpatrick types 4–6 light coloration of the fibrous cephalic plaque or the shagreen patch may be hyperpigmented, which obscures erythema [153, 154].

The extracutaneous clinical features include multiple retinal hamartomas, cortical dysplasias, subependymal nodules (SEN), subependymal giant cell astrocytomas (SEGA), cardiac rhabdomyoma(s), lymphangioleiomyomatosis (LAM), or angiolipomas (≥2). When angiolipomas and LAM overlap regionally, they are considered to meet a single criterion. Cystic lung lesions in association with LAM are noted in 30–40 % of adult females, but only 10–20 % of adult males [152, 153].

Minor criteria include one cutaneous "confetti" skin lesion and two oral (dental enamel pits (>3) and intraoral fibromas (≥2)) and three systemic-retinal achromic patches, multiple renal cysts, or nonrenal hamartomas. Confetti lesions are guttate areas of hypopigmentation and are most accurate in the youngest of patients, as older patients may experience guttate hypomelanosis in response to trauma or cumulative photodamage [152, 153].

One population of color that was evaluated regarding manifestations of TS was a Japanese group of 166 patients. In that cohort, the frequency of cutaneous manifestations was angiofibromas 93 %, shagreen patch 83 %, ungula fibromas 64 %, forehead plaque 46 %, and hypomelanotic macules (>3) 65 %. This latter finding could be due to light skin tone and lack of Wood's lamp analysis for these patients, but based on the trend toward reduction of the finding with age 80 %+ for 0–9 years and 30 % for 60–69 years, it appears that hypomelanotic macules become less notable with age in TS. Ungual fibromas follow the reverse course. Less than 5 % of 0–9 years have them, while almost 100 % of patients aged 70–79 years manifest with them. Angiofibromas appear stable in incidence through time. Furthermore, it should be noted that in this cohort 39 % had no identifiable TSC 1or TSC2 mutation [156].

Other cutaneous tumors that have been described in patients with TS include epidermoid cysts. Tuberous sclerosis has been described to occur in a mosaic pattern. Additionally, a new hamartoma has recently been described in a multinational cohort, termed folliculocystic and collagen hamartoma of tuberous sclerosis complex, which histologically has fibrosis around follicles extending to the fat and excess collagen with some patients having comedones and features of ruptured cysts. Five out of six patients reported had TS [157].

Treatment

- **Cutaneous examination annually can help identify diagnostic features and identify children in susceptible families early.**
- **Currently tuberous sclerosis is observed clinically for changes requiring therapeutic interventions including ophthalmologic, neurologic, dental, cardiac, genetic, renal, and pulmonary** [151–155]**.**

Conclusions

Hypopigmentation in children can have a broad causation. Careful attention to age of onset, lesion morphology and progression over time is needed to identify the correct diagnosis and provide the correct therapies and/ or anticipatory guidance.

Conflict of Interest The authors report no relevant conflicts of interest in this work.

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Mongolian Spots

6

Eulalia Baselga

Abstract

Mongolian spots are congenital dermal melanocytosis usually on the lumbosacral area and buttocks. Therapy is usually unnecessary because they tend to fade with age. When extensive and especially extending to the ventral surface, storage diseases may be considered.

Keywords

Mongolian spot • Phakomatosis pigmentovascularis • Phakomatosis pigmentopigmentalis • Mucopolysaccharidosis type II

Introduction

Mongolian spots are congenital, benign blue-gray or blue-black patches that represent dermal melanocytosis [1].

Epidemiology

- **Mongolian spots are one of the most common birthmarks**
- **There are racial differences in their incidence.**

Mongolian spots are very common being present in more than 90 % of African and Asian infants, and less common in Caucasian (10 %) [1–3]. The reason for such racial differences is unknown.

Clinical Features

- **Single or multiple blue-gray macules and patches**
- **Most common in lumbosacral area and buttocks**
- **Fade in the first years of life**
- **May be associated with lysosomal storage diseases**
- **May be part of phakomatosis pigmentovascularis (*Cesioflammea*) or phakomatosis pigmentopigmentalis**

Mongolian spots appear as large blue-gray or black-gray macules or patches of different sizes up to several cm and can be single or multiple. They may round or oval, but they often have a geographic outline. They may occur anywhere, but the areas of predilection are the lumbosacral areas and buttocks (Figs. 6.1 and 6.2). Those outside the lumbosacral areas have been sometimes named aberrant Mongolian spots (Fig. 6.3). With age they tend to fade in color and usually they are not visible by the school age [1]. Extrasacral and dark colored Mongolian spots sometimes persist into adulthood.

Mongolian spots may be seen in association with capillary malformation (port-wine stains) in the so-called phakomatosis cesioflammea (Fig. 6.4) or with segmental cafe au lait macules (phakomatosis pigmentopigmentalis) [4, 5].

Extensive Mongolian spots may be a manifestation of GM1 gangliosidosis and mucopolysaccharidosis type I (Hurler's disease), and less commonly mucopolysaccharidosis type II (Hunter's syndrome), mucolipidosis, Niemann–Pick disease, and mannosidosis [6, 7]. In these cases of associated lysosomal storage diseases Mongolian spots usually involve both the dorsal and ventral trunk, in addition to the skin of the sacrum and extremities, and may be progressive in nature [7].

Biopsy of Mongolian spots shows elongated and stellate melanocytes in the reticular dermis.

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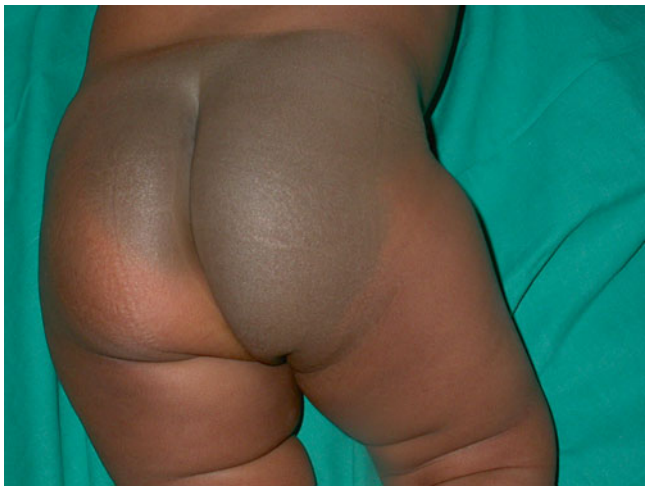

Fig. 6.1 Mongolian spot in the most common location: lumbosacral and buttock area

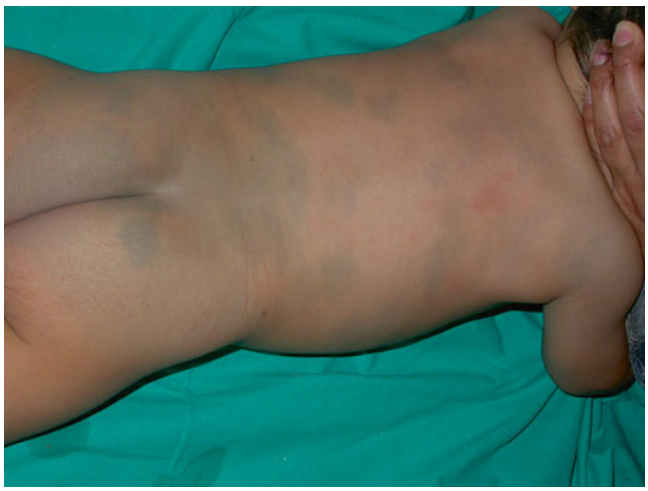

Fig. 6.2 Extensive Mongolian spot

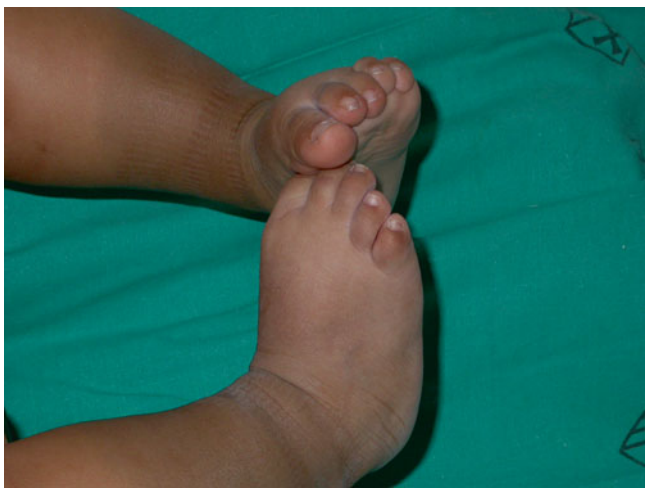

Fig. 6.3 Mongolian spot on the extremity. These Mongolian spots in locations other than the lumbosacral area have been called *aberrant Mongolian spots*

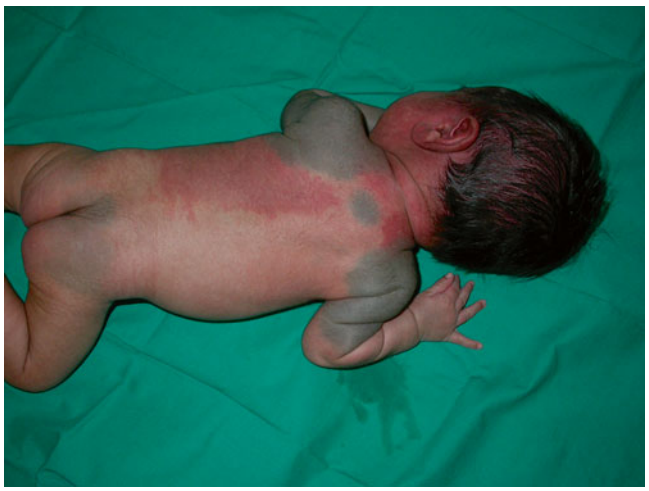

Fig. 6.4 Phakomatosis pigmentovascularis (cesioflammea). The coexistence of Mongolian spot and capillary malformation (nevus flammeus)

Pathogenesis

Mongolian spots probably represent abnormal migration of melanocytes from the neural crest to the epidermis. The cause of Mongolian spots is unknown.

Treatment

- **No treatment is usually needed**

Therapy is usually unnecessary because Mongolian spots are benign lesions and tend to fade with age. There is a report on the use of Q-switched alexandrite laser and also of intense pulsed light treatment with some success [8–11]. Treatment of lesions in children of color should be undertaken carefully as the risk of hyperpigmentation and hypopigmentation with laser therapies can be quite high, especially with Fitzpatrick type V and VI patients.

Prognosis

Mongolian spots are benign. When associated with lysosomal storage diseases the prognosis is that of the associated disorder.

Conclusion

Mongolian spots are very frequent and usually benign. When extensive and especially if they involve both the ventral and dorsal surface storage diseases should be considered. It can be also an early sign of neurometabolic diseases, in particular lysosomal storage disorders. The presence of extensive dermal melanocytosis should alert the physician to the presence of such disorders, making early diagnosis possible [12].

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Nevus of Ota and Nevus of Ito

7

Eulalia Baselga

Abstract

Nevus of Ota and nevus of Ito are uncommon sporadic forms of dermal melanocytosis. They may be associated with capillary malformations. In rare cases malignant melanoma may develop in the skin or the uvea. GNAQ mutations have been detected in some. Some degree of lightening can be achieved with lasers.

Keywords

Nevus of Ota • Nevus of Ito

Introduction

- Nevus of Ota and nevus of Ito are two types of dermal melanocytosis that differ in distribution.

Nevus of Ota (*naevus fusco-caeruleus ophthalmomaxillaris*) and nevus of Ito (*naevus fusco-caeruleus acromiodeltoideus*) are uncommon forms of dermal melanocytosis with a particular distribution: nevus of Ota along the distribution of the ophthalmic and maxillary branches of the trigeminal nerve including the sclera of the eye (Fig. 7.1) and nevus of Ito distributed in the posterior supraclavicular, scapular, or deltoid regions [1] (Fig. 7.2).

Epidemiology

- **Nevus of Ota and nevus of Ito are sporadic**
- **They are more common in Asian and African-American children**
- **Nevus of Ota is five times more common in females.**

Nevus of Ota and nevus of Ito are sporadic lesions more common in Asians and African Americans and are up to five times more common in females [2, 3]. The incidence of nevus of Ota in darker skin has been estimated to be around 0.016 % [4]. Nevus of Ito is less frequent and the exact incidence is unknown.

Clinical Features

- **Nevus of Ota and nevus of Ito are speckled, irregular blue-gray macules in a characteristic distribution**
- **Nevus of Ota affects the ophthalmic and maxillary branches of the trigeminal nerve including the sclera of the eye**
- **Nevus of Ito affects the posterior supraclavicular, scapular, or deltoid regions**
- **They may be present at birth or appear later**
- **They may be associated with capillary malformations (port-wine stains) in phakomatosis pigmentovascularis type II**

Nevus of Ota and nevus of Ito present as bluish to gray irregularly shaped and sometimes speckled macules. They are usually present at birth, although in as much as 40 % of cases the onset is at puberty [1, 3]. Nevus of Ota usually affects the periorbital region, temple, forehead, malar region, and/or nose. The ipsilateral sclera may be pigmented in two-thirds of cases and may also affect the ipsilateral iris,

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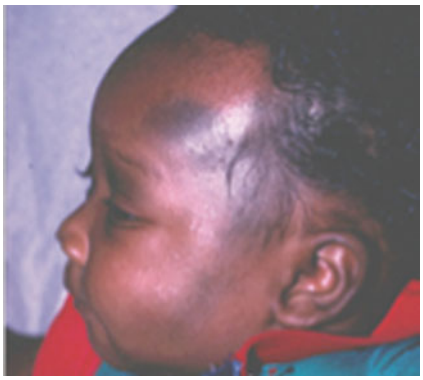

Fig. 7.1 Nevus of Ota affecting the temple, maxillary area, and sclera of the skin

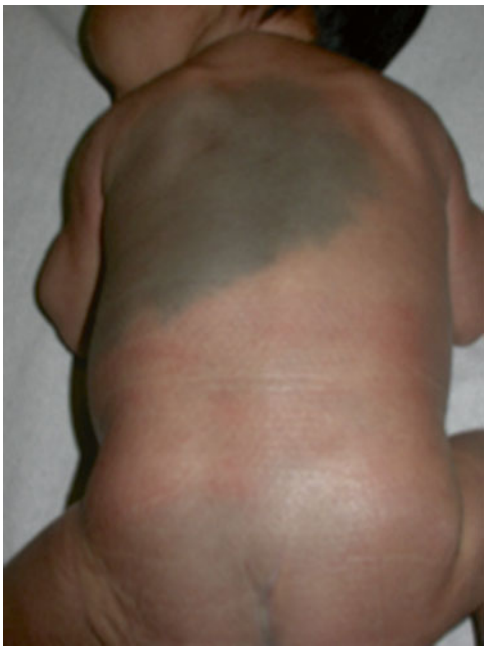

Fig. 7.2 Nevus of Ito

conjunctiva, retina, cornea, choroid, extraocular muscles, and retrobulbar fat. Oral mucous membranes and palate may be involved. It is usually unilateral though at times bilateral cases may occur. The nevus of Ito involves the area supplied by posterior supraclavicular and lateral cutaneous brachial nerves which are the side of the neck, the supraclavicular and scapular areas, and shoulder region. Nevus of Ota nevus of and Ito are usually unilateral, but they may be bilateral and coexistence of nevus of Ito and Ota in the same patient has been described [5].

Nevus of Ota and Ito may also coexist with capillary malformations in the so-called phakomatosis pigmentovascularis or cesioflammea. Coexistence with nevus spilus has also been reported [6].

Pathogenesis

It is believed that nevus of Ota and nevus of Ito are the result of a failure of migration of the melanocytes from the neural crest to the epidermis. They are histologically characterized by the presence of melanin-producing dendritic melanocytes within the upper and mid-dermis with their axis parallel to the skin surface. The overlying epidermis is normal. Recently mutations in GNAQ have been detected in some and other congenital dermal melanocytosis [7].

Treatment

- **Q-switched laser treatment of nevus of Ota and Ito is possible.**
- **Many treatments are necessary and repigmentation may occur.**

Treatment of nevus of Ota and Ito may be considered for cosmetic reasons, particularly if the patient is bothered by the appearance of the lesion. They may be treated with Q-switched ruby, alexandrite, or Nd:YAG lasers [8–10]. Multiple sessions in the range of 7–10 or more are usually needed. Repigmentation after years is the main caveat. The earlier the treatment is given the more rapid clearing but also the higher recurrence rate. Dermabrasion and cryotherapy have also been used although there is a risk of scarring and therefore are not generally recommended [11, 12]. Dyspigmentation in the form of hyperpigmentation and/or hypopigmentation can occur with laser therapy in patients of color, especially children with Fitzpatrick types IV or greater.

Prognosis

Nevus of Ota and nevus of Ito are benign dermal melanocytosis; however there are rare cases of malignant melanoma developing on nevus of Ota of fair-skinned persons and even more exceptionally on nevus of Ito [13, 14]. Melanomas that develop on these nevi do not usually follow the ABCD rule of malignant melanoma but present as subcutaneous masses [13]. Uveal melanomas may contain a GNAQ mutation and it has been hypothesized that GNAQ mutations may account for the association between nevus of Ota and uveal melanoma [7].Uveal melanomas with a high risk of metastases may occur in an estimated rate of 1/400 nevus of Ota [15]. Therefore it is recommended that all patients with oculodermal undergo ophthalmic examination with ocular pressure checks and one reference suggested mapping with optical coherence tomography on a twice-yearly basis [15].

Ongoing Research

There has been recent research on the sequential use of different lasers in the treatment of dermal melanocytosis [16]. Also GNAQ mutations in nevus of Ota and Ito have to be further investigated [7].

Conclusion

Nevus of Ota and nevus of Ito are two variants of dermal melanocytosis with different locations that are more common in Asians and African Americans. In nevus of Ota periodic ophthalmologic examination for early detection of melanoma and also glaucoma is recommended.

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Pigmentary Mosaicism

8

Eulalia Baselga

Abstract

Pigmentary mosaicism refers to hyper or hypopigmentation due to genetic heterogenecity of cells. Pigmentary mosaicism may follow any of the patterns of cutaneous mosaicism and persist through life. Diagnosis is clinical. Associated extracutaneous manifestations have been reported in as much as 30 % of the cases.

Keywords

Pigmentary mosaicism • Blaschko lines • Linear and whorled nevoid hypermelanosis

Introduction

- **Pigmentary mosaicism refers to hyper- or hypopigmentation due to genetic heterogenecity of cells.**
- **It has been referred to by many different names such as linear and whorled nevoid hyperpigmentation, segmental pigmentary disorder, nevoid hypermelanosis, or patterned pigmentation.**

Pigmentary mosaicism is a term that has been used to describe variegate or irregular hyperpigmentation or hypopigmentation due to genetic heterogenecity of the cells that compose the skin. In this chapter we are going to focus on mosaic hyperpigmentation only. A mosaic state is the proposed pathogenetic mechanism of this type of hyperpigmentation although it has not been probed in all cases. Therefore some authors prefer the term patterned hyperpigmentation [1]. Pigmentary mosaicism may present conforming to the different patterns of cutaneous mosaicism as described by Happle [2].

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Epidemiology

- **The exact incidence in dark-skinned individual is not known**

There are no exact figures regarding the frequency of pigmentary hypermelanosis in dark skin. For any race the frequency also depends on the pattern. Phylloid hypermelanosis is the rarer variant with only a few cases published [3, 4].

Pigmentary mosaicism is usually not inherited although a few cases with several affected members in the same family point to epigenetic mosaicism (autosomal monoallelic expression) to explain the familial occurrence [5–7].

Clinical Features

- **Pigmentary mosaicism may follow any of the patterns of cutaneous mosaicism**
- **May not be apparent at birth and increase for a few years until it stabilizes.**
- **Many different extracutaneous abnormalities (CNS, ocular, cardiac, skeletal) have been described and investigation should be directed by clinical findings**

Pigmentary mosaicism manifests as hyperpigmented macules and patches that follow different patterns. They are usually present at birth although they may not become apparent until sun exposure during the first summer and may increase in number and size during the first years of life. The color may

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vary from light to dark brown. The patterns that have been described are linear and whorled hypermelanosis in which hyperpigmented, reticulated, streaky, narrow, and whorled macules occur along Blaschko lines (Fig. 8.1); broad band of hyperpigmentation along Blaschko lines; patchy hyperpigmented irregularly shaped macules without midline separation; checkerboard pattern, with alternating squares of pigmentary anomalies with a sharp midline separation and sometimes with a flag-like distribution (Fig. 8.2a, b) [8]; and lateralization pattern in which hyperpigmented macules affect only one side with midline separation (Table 8.1) [2, 9].

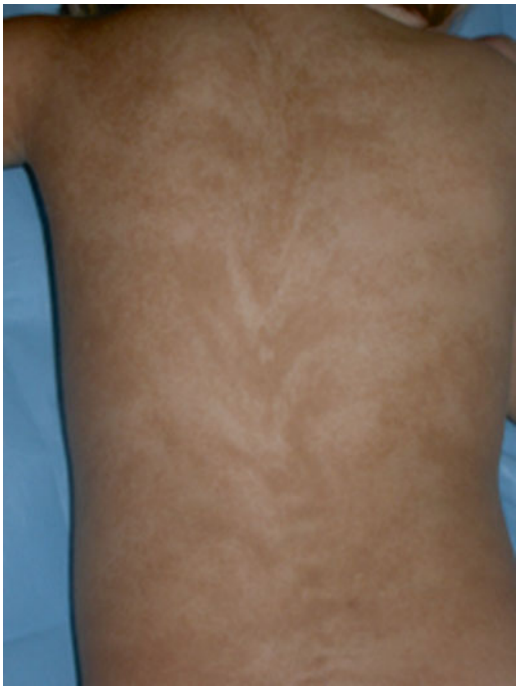

Fig. 8.1 Linear and whorled nevoid hypermelanosis. A form of pigmentary mosaicism that follows the lines of Blaschko

Associated extracutaneous manifestations have been reported in as much as 30 % of the cases, although this figure may reflect a reporting bias [10]. The associated findings include developmental delay, autism, seizures, microcephaly, and ocular, cardiac (ventricular septal defects and tetralogy of Fallot), and skeletal abnormalities (digit abnormalities, hemiatrophy).

The associated anomalies are so diverse that clinical investigation should be directed by clinical findings.

Pathogenesis

An enormous range of cytogenetic abnormalities has been reported in PM, including polyploidy, aneuploidy, and chromosomal deletions, insertions, and translocations. Mosaic trisomy 20, 7, 14, 18, and X-chromosomal have been reported in linear and whorled nevoid hypermelanosis [11–13]. The cytogenetic abnormalities may be only be found in fibroblast of affected skin. There is no single genotype for each phenotypic expression of pigmentary mosaicism except may be for phylloid hypermelanosis that has been more consistently related to chromosome 13 aberrations or mosaic chromosome 5p tetrasomy [4, 14] In most cases of pigmentary mosaicism a cytogenetic alteration cannot be detected and several hypotheses have been proposed to explain the abnormal pigmentation, such as comigration of genetically different cell populations, X-chromosome functional disomy,

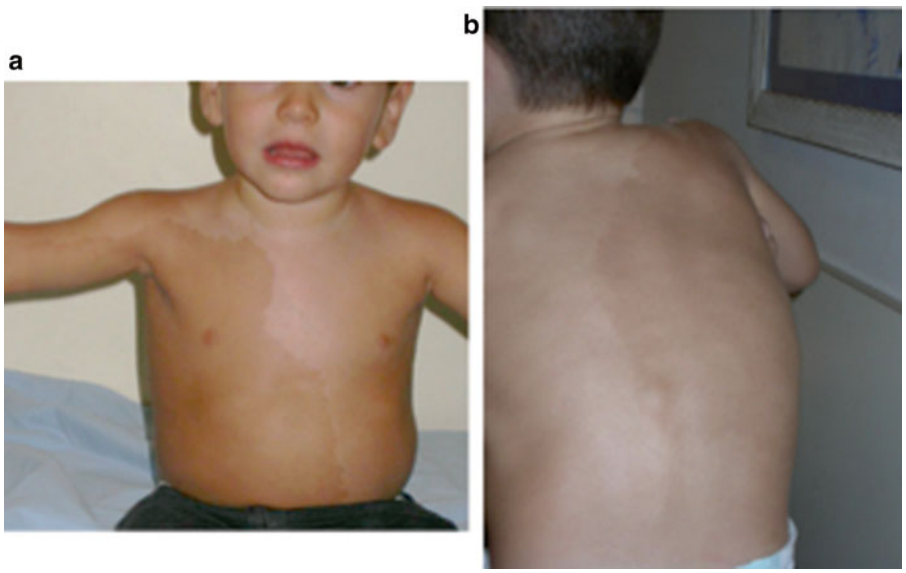

Fig. 8.2 Pigmentary mosaicism in a lateralization pattern. (**a**) Front view and (**b**) back view

Table 8.1 Patterns of pigmentary mosaicism

Patterns of pigmentary mosaicism	Clinical features
Linear and whorled hypermelanosis	Reticulated, streaky, narrow and whorled macules occur along Blaschko lines
Broad band Hyperpigmentarion	Broad band of hyperpigmetation that follow Blaschko lines
Patchy hyperpigmentation	Irregularly shaped macules without midline separation
Checkerboard pattern	Alternating squares of pigmentary anomalies with a sharp midline separation or arranged in a flag-like pattern
Lateralization pattern	Hyperpigmented macules affect only one side with midline separation

"Spreading" of X inactivation to autosomes, transposons, genetic imprinting, and phenotypic reversion [15].

Histology usually shows hyperpigmentation of the basal keratinocytes with normal number of melanocytes.

Treatment

- **No effective treatment has been described**

There is no effective treatment for pigmentary mosaicism.

Prognosis

The hyperpigmented macules persist throughout life. The prognosis is marked by the associated extracutaneous findings.

Conclusion

Pigmentary mosaicism is a common usually sporadic disorder. Many different names have been used to describe it due to the fact that clinically it may manifest in any of the five patterns of cutaneous mosaicism described by Happle [9].

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Ashy Dermatosis or Erythema Dyschromicum Perstans

9

Lynn Yuun Tirng Chiam

Abstract

Ashy Dermatosis is an acquired disease of dermal pigmentation of unknown origin. Rarely, it can affect children presenting with slate-gray macules affecting the neck and trunk. There is no effective treatment. Unlike adults, childhood Ashy dermatosis is likely to improve significantly.

Keywords

Ashy dermatosis • Melanophages • Erythema dyschromicum perstans • Slate-gray macules

Introduction

- An acquired disorder of dermal pigmentation
- Presents with slate-gray macules
- Common in the Hispanic population

Ashy dermatosis or erythema dyschromicum perstans (EDP) was first described by Oswaldo Ramirez in 1957 [1]. It is an acquired disorder of dermal pigmentation of unknown origin characterized by asymptomatic slate-gray oval macules. Most cases of EDP have been described in adults and occur in the second decade of life. Adult EDP is more commonly seen in the Hispanic population but has been described in the Caucasian, Japanese, Indian, and African-American population. Children with EDP are uncommon making up 8 % of the total number [2].

Epidemiology

- **Childhood EDP accounts for 8 % of the cases**
- **Affects all ethnic groups**
- **Female preponderance**

To date, 45 children with EDP have been described [2–9]. Although adult patients with EDP are more likely to be of Hispanic descent, more than half, 26 children with EDP, are Caucasian. Hispanic, Indian, Japanese, and African-American children have also been reported [2, 4–7, 9]. Unlike adults, there is a female preponderance with a female-to-male ratio of 1.5:1. However among the non-Caucasian children, a higher proportion were females (85 %) as compared to Caucasian children (48 %).

Clinical Presentation

- **Affects neck and trunk**
- **Asymptomatic**
- **Etiology is unknown**

The age of onset varied between less than 1 and 11 years, with the vast majority (77 %) having an onset between 5 and 10 years of age.

Patients with EDP have oval to irregular ashy gray to lead-colored macules affecting the body symmetrically. Unilateral distribution is rare [4]. They range from 0.5 cm to several centimeters and are normally asymptomatic.

Initial lesions may have erythematous and indurated borders. As they progress, the erythematous borders are lost and are sometimes replaced by hypopigmented edges. In most cases, there is no evidence of erythema upon diagnosis. Much of the dyspigmentation occurs on the neck (Fig. 9.1) and trunk and may spread to involve the face (Fig. 9.2) and

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limbs (Fig. 9.3). The palms, soles, scalp, nails, and mucous membranes are usually spared [1, 10–13].

The etiology of EDP remains unknown although several associations have been noted including benzodiazepines [14, 15], thyroid disease [16, 17], environmental allergens such as the pesticide chlorothalonil [18], toxins such as ammonium nitrate [19], and the fungicide fusilade [17].

Histopathology of the inflammatory border may demonstrate lichenoid dermatitis with vacuolization and necrosis of basal cells and occasional colloid bodies. The papillary dermis is edematous with incontinence of the pigment and shows a mild-to-moderate inflammatory lymphohistiocytic infiltrate intermingled with melanophages [20].

EDP can be differentiated from fixed drug eruption from its gray color, lack of underlying drug trigger, absence of eosinophilia, and less extensive basal layer hydropic degeneration.

In argyria, the mucous membrane and sun-exposed areas are affected and histology shows distinct gray-brown granules in macrophages and adnexal structures.

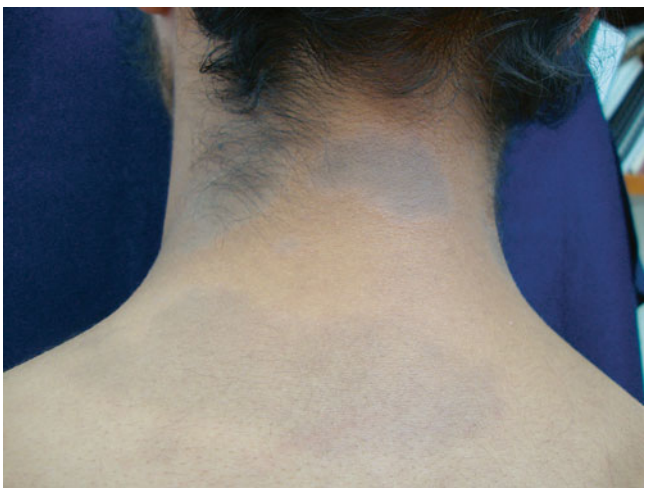

Fig. 9.1 *Slate-gray* patches affecting the neck (courtesy of Carola Duran McKinster, MD)

Prognosis

- **No treatment has been consistently effectively for EDP**
- **Childhood EDP likely to have significant improvement**
- **Sun protection is advised**

Although EDP is unlikely to resolve in adults [1, 10, 13–16, 19, 21–29], an eventual improvement or resolution of the lesions is more often observed in children. The majority of prepubertal patients will be expected to experience significant improvement after 2–3 years [2, 9] and recurrences have never been reported after clearance. No treatment has been consistently effective for EDP and it is recommended to use sun protection to avoid lesional prominence until the lesions clear. Topical steroids and hydroquinones are not useful. Recently, dapsone and clofazimine have been reported to prevent disease progression in adults [12, 17, 30]. Other anecdotal reports have used oral corticosteroids, tetracyclines, ultraviolet light, isoniazid, and griseofulvin.

Summary

Unlike adult EDP, childhood EDP is less common in non-white populations. It tends to affect the truck and proximal extremities. The etiology is not well understood and no therapy has been used successfully to treat EDP. However, in childhood EDP, there is a good chance of complete clearance with time.

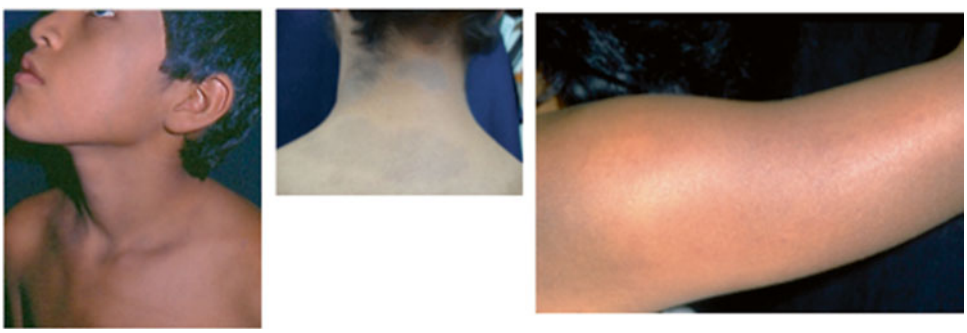

Fig. 9.2 *Ashy gray* macules and patches affecting the face and neck (courtesy of Carola Duran McKinster, MD)

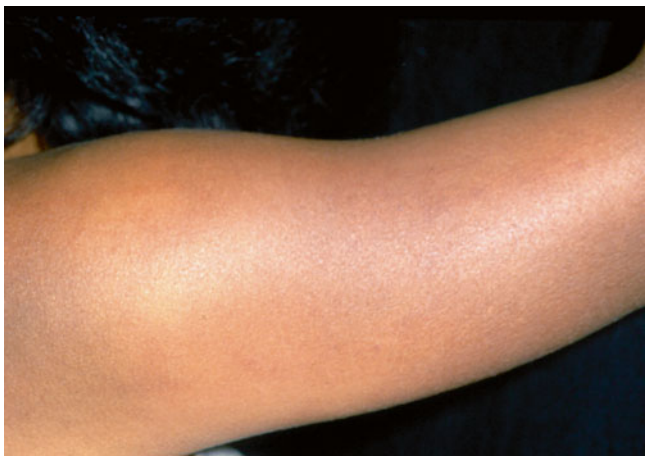

Fig. 9.3 *Gray* to *lead*-colored patches affecting the upper arm (courtesy of Carola Duran McKinster, MD)

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Confluent and Reticulate Papillomatosis (of Gougerot–Carteaud Syndrome)

10

Lynn Yuun Tirng Chiam

Abstract

Confluent and reticulate papillomatosis (CRP) is a rare dermatosis characterised by hyperpigmented confluent patches and papules localised to the seborrhoeic areas of the trunk. This disorder is often recalcitrant with variable response to treatment.

Keywords

Confluent and reticulate papillomatosis • Hyperpigmentation • Malassezia furfur

Introduction

- **Pathophysiology poorly understood**
- **Considered to be an abnormal host reaction to Malassezia furfur**
- **Set of criteria proposed**

Confluent and reticulate papillomatosis (Confluent and Reticulated Papillomatosis of Gougerot and Carteaud, CRP) is a rare condition first described by Gougerot in 1927 [1]. The pathophysiology of CRP remains poorly understood, but it is considered to be an abnormal host reaction to *Malassezia furfur* [2]. It usually affects teenagers and young adults with a predilection for the upper chest and trunk. CRP has been described in all ethnic groups including Whites, Asians, Indian, Middle Eastern, and African Americans [3]. Recently, a set of criteria for the diagnosis of CRP have been proposed [3]. See Table 10.1.

Epidemiology

- **Occurs after puberty**
- **Present for years before diagnosis**
- **No gender predilection**

CRP is an uncommon skin condition with an incidence among Lebanese population of 0.02 % in a clinic-based study [4]. Most patients have the lesions for many months to years, and the majority have disease onset after puberty. At presentation, the skin eruption has usually been present for 1–4 years. The age at onset of skin eruption ranged from 8 to 32 years [3, 4] with the mean age of 15 years noted in one study [3]. There is no gender predilection.

Clinical Presentation

- **Tan to brown scaly macules, patches, and plaques**
- **Asymptomatic**
- **Seborrhoeic areas of trunk**

Skin lesions consist of reticulated, hyperpigmented tan to brown macules, patches, and plaques that are confluent centrally on the chest (especially intermammary on the chest) and back, with reticulation of lesions as they extend away from the midline (Fig. 10.1). In the majority of cases, scales are present. In many patients, mild erythema is also described; however, this may be obscured by dark pigmentation in patients who are Fitzpatrick types V and VI. The most common areas involved include the chest, shoulders, neck, axilla, and back. CRP can unusually affect the face and feet. A vast majority of the patients are asymptomatic while a few complain of pruritus.

The main differential diagnoses to consider are acanthosis nigricans, tinea versicolor, seborrhoeic dermatitis, epidermal nevus, verruca plana, SCURF (dirt), and Darier's disease.

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Table 10.1 Criteria for diagnosis of CRP

Scaling brown macules and patches, at least part of which appear reticulated and papillomatous
Involvement of upper trunk and neck
Fungal staining is negative for fungus
No response to antifungal treatment
Excellent response to minocycline

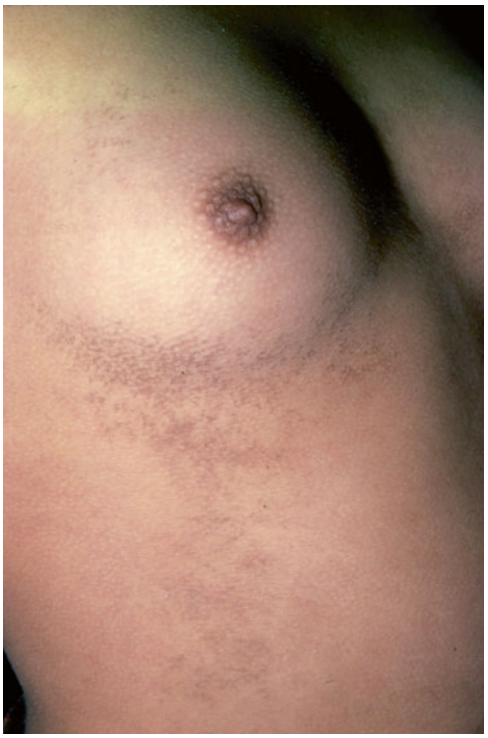

Fig. 10.1 Reticulated *brown* patches over the chest (courtesy of Prof Ruiz-Maldonado)

Histopathological findings are consistent with a hyperproliferative disorder. Epidermal changes include hyperkeratosis, papillomatosis, variable acanthosis, and sparse dermal inflammation (Fig. 10.2). Some reports have demonstrated the presence of both yeast and hyphae in association with CRP [4–7].

Pathogenesis

- **Not well understood**
- **May be regarded as a genetic disorder of keratinisation with abnormal response to *Malassezia Furfur***

The cause of CRP is not fully known. The main theory that has been advocated is that this entity results from an abnormal host reaction to *Malassezia furfur* [2]. Other proposed causes include endocrine imbalance and UV exposure [8].

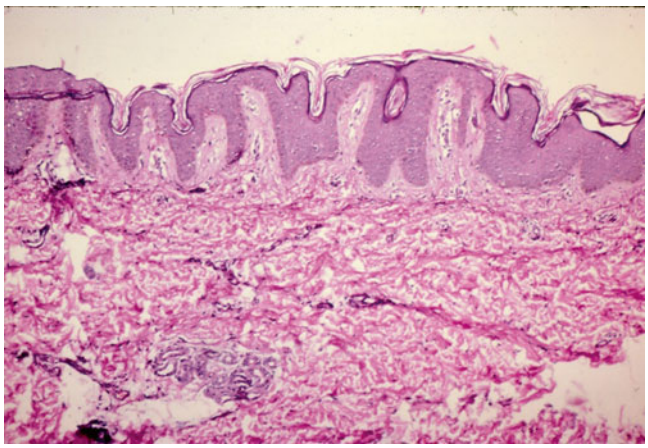

Fig. 10.2 Photomicrograph showing mild orthokeratotic hyperkeratosis, marked papillomatosis, variable acanthosis, and sparse dermal inflammation cells. Haematoxylin and eosin ×40

Genetic susceptibility has been suggested in case reports of familiar CRP [9, 10]. It is been thought that CRP may be regarded as a genetic disorder of keratinisation with an abnormal response to secondary colonisation to *M. furfur*.

Treatment

- **Minocycline treatment of choice**
- **Require 1–3 months of treatment**
- **Mediate changes through anti-inflammatory actions**

Carteaud proposed that antibiotics might help [11]. Good response to minocycline has been noted in many studies [3, 12–17] and is considered the treatment of choice. Minocycline was given for 1–3 months with a vast majority achieving complete clearance. Recurrence after stopping minocycline had been documented in some patients. It is believed that antibiotics mediate changes through their anti-inflammatory actions rather than antibacterial actions. In contrast, there is poor response to antifungals. Other beneficial medications include isotretinoin [18], topical tretinoin [19], topical tazarotene [20], calcipotriol [21], selenium sulphide [6], tacalcitol [22], and tacrolimus. Tinea versicolour will sometimes co-exist with the condition and potassium hydroxide preparation can be helpful in identifying patients who would benefit from topical antifungal therapy.

Summary

CRP is a poorly recognised and understood disorder which affects teenager predominantly. The brown pigmentation on the upper trunk is often asymptomatic but is a cosmetic problem. It commonly remains undiagnosed for a few years and minocycline is the treatment of choice.

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Idiopathic Eruptive Macular Pigmentation

11

Ramón Ruiz-Maldonado and Carola Durán-McKinster

Abstract

Idiopathic eruptive macular pigmentation is an uncommon disorder of cutaneous hyperpigmentation of unknown etiology. It affects mainly children and teenagers with both genders equally affected. Asymptomatic brown macules affecting the neck, trunk, and proximal extremities are characteristic with pigmentation in various tones of brown: light dark to dark brown macules. Lesions usually appear abruptly without history of preceding inflammatory lesions or previous drug exposure. The surface of most macules is not different from the uninvolved skin, although some lesions may have a velvety surface. Mucous membranes and nails are spared. A biopsy of a pigmented spot shows an increased number of melanocytes in the basal-cell layer of the epidermis and prominent melanophages in the papillary dermis, without visible basal layer damage or lichenoid inflammatory infiltrate. A mild perivascular, lymphocytic, and histiocytic infiltrates may be present. Differential diagnosis with erythema dyschromicum perstans (EDP) or "ashy" dermatosis which is characterized by a slowly progressive, occasionally pruritic ash-colored hyperpigmentation, mainly in adults, and histologic changes presents basal layer vacuolization and apoptotic bodies. Prognosis is good in all cases. Treatment is unnecessary; in most cases, slow gradual and spontaneous disappearance of the lesions during several months to years is the rule.

Keywords

Idiopathic eruptive macular pigmentation • Ashy dermatosis

Background/Introduction

- **Idiopathic eruptive macular pigmentation is an uncommon disorder of cutaneous hyperpigmentation.**
- **The etiology remains unknown.**
- **The condition appears to be a distinct clinicopathologic and histologic entity.**

The term idiopathic eruptive macular pigmentation (IEMP) was initially coined by Degos et al. in 1978 [1]. They reported seven cases of a pigmented dermatosis and considered the condition different from erythema dyschromicum perstans.

The etiology of IEMP remains unknown. Hyperpigmentation has no apparent cause although two cases following pityriasis rosea were reported [2].

Epidemiology/Demographics

- **IEMP is a very rare and maybe an underreported condition.**
- **Children and teenagers are most affected.**

This condition, which affects mainly children and teenagers with both genders equally affected, is less commonly observed in adults [3, 4], and an isolated case was reported associated with pregnancy [5].

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The alleged rarity of IEMP may be partially caused by medical unfamiliarity with this entity, despite its clinical and histopathologic picture. During a 9-year period at the Asian Medical Center, in Seoul, Korea, only ten cases were seen. The age of onset varied from 1 to 20 years. Skin lesions of eight patients were multiple brown macules involving the trunk, face, neck, and extremities. In two patients, multiple dark brown macules and patches were noted [6]. Caucasian patients may be affected as well: five patients were studied in France, and at the onset of the disease, the patients were 2–16 years of age [7].

Clinical Presentation

- **Asymptomatic brown macules affecting the neck, trunk, and proximal extremities are characteristic**
- **Pigmentation presents in various tones of brown: light dark to dark brown macules**
- **Lesions usually appear abruptly without history of preceding inflammatory lesions or previous drug exposure**

IEMP is an unusual condition of cutaneous pigmentation in various tones of brown: light **dark** to brown macules of discrete, round to oval lesions measuring from a few millimeters (Fig. 11.1) to several centimeters. The pigmentation is not influenced by sun exposure. Most lesions are located in the neck, trunk, and proximal limbs (Fig. 11.2). The lesions usually appear abruptly without history of preceding inflammatory lesions and absence of previous drug exposure. The surface of most macules is not different from the uninvolved skin, although some lesions may have velvety or mildly elevated surfaces [3, 8]. Mucous membranes and nails are spared.

Treatment of IEMP is unnecessary because in most of the cases, spontaneous disappearance of the lesions over several months to years seems to be the rule. The disease does not relapse. An unusual case of a 24-year-old woman with IEMP lasting 21 years characterized by several periods of spontaneous resolution followed by recurrences was reported [9].

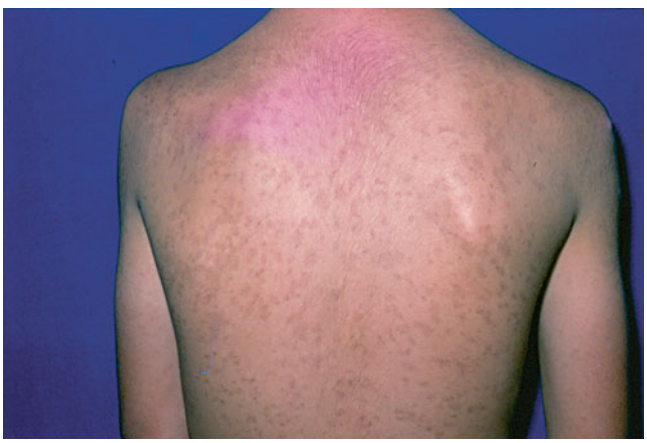

Fig. 11.1 Multiple hyperpigmented macules

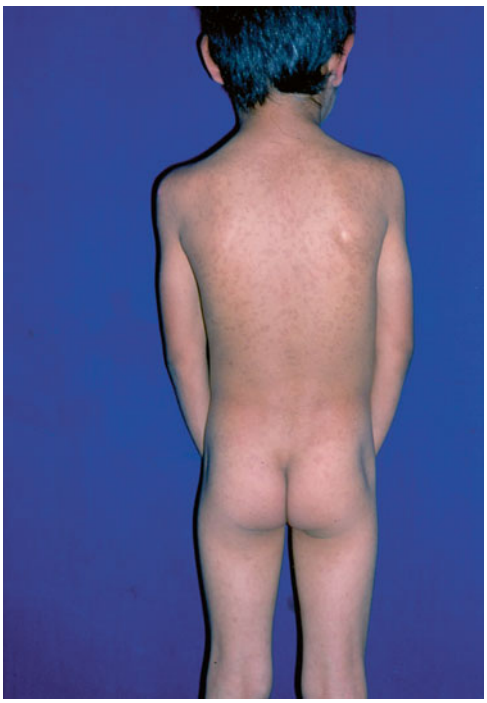

Fig. 11.2 Hyperpigmented macules without erythema

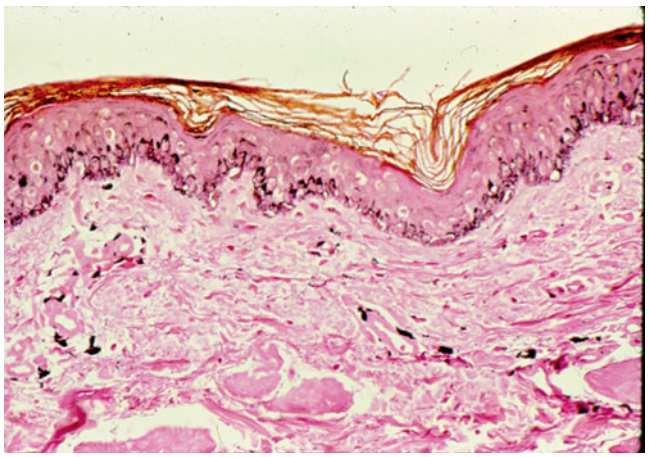

Fig. 11.3 Skin biopsy reveals increased number of melanocytes in the epidermis (silver stain ×10)

At the beginning, tentative diagnoses are usually ashy dermatosis (erythema dyschromicum perstans), fixed drug eruption, or mastocytosis. The diagnosis of IEMP is based on the absence of history of any erythema, and drug medication as well as the absence of Darier's sign.

Histopathology is seldom justified and the histological picture is not specific. The biopsy of a pigmented spot shows an increased number of melanocytes in the basal-cell layer of the epidermis (Fig. 11.3) and prominent melanophages in the papillary dermis, without visible basal layer damage or lichenoid inflammatory infiltrate (Fig. 11.4). A mild perivascular, lymphocytic, and histiocytic infiltrate may be present. Mast cells are not found. The histopathological study from velvety

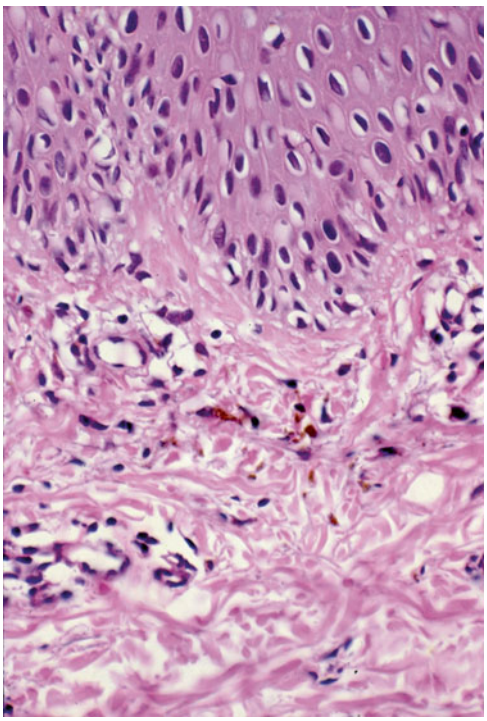

Fig. 11.4 Prominent melanophages in papillary dermis without basal layer damage (H/E × 20)

lesions of nine Indian patients, seven males and two females aged 6–14 years, showed papillomatosis of the dermis with prominent pigmentation of the basal layer (pigmented papillomatosis) without any significant dermal inflammation. Two cases had spores of *Pityrosporum ovale* in the thickened horny layer, one of which also had bacterial colonies in the stratum corneum [10].

Electron microscopy shows keratinocytes of the basal and suprabasal layers filled with large numbers of mature and clustered melanosomes. Keratinocytes of all epidermal layers appeared otherwise normal. The number and aspect of melanosomes in melanocytes were normal, as was the overall appearance of melanocytes. In the papillary dermis, macrophages contained large aggregates of melanosomes [7].

Differential diagnosis includes erythema dyschromicum perstans (EDP) or "ashy" dermatosis which was described by Ramirez [11] as a peculiar, slowly progressive, occasionally pruritic ash-colored hyperpigmentation, which leaves a permanent discoloration. It occurs most frequently in Central and South America, mainly in adults, but the condition was reported in 14 Caucasian prepubertal children in Spain by Torrelo et al. [12]. Histologic changes include basal layer vacuolization, apoptotic or cytoid bodies, edema of the dermal papillae, a mild dermal lymphohistiocytic infiltrate, and pigment in dermal macrophages. Peripherally located lichenoid changes can be observed. The authors suggest that EDP is a distinctive clinical entity, different from lichen planus, but may be identical to the so-called idiopathic eruptive macular pigmentation.

Prognosis

- Is good in all cases.

The eruption is asymptomatic and the patients are otherwise healthy. Results of physical examination and routine laboratory tests are within normal limits. Spontaneous fading of the pigmentation occurs gradually without any treatment.

Conclusion

Despite the scarcity of reported cases, IEMP is not extremely rare in pediatric practice especially in Hispanic and Asian patients. This entity should be distinguished from other disorders of pigmentation in childhood and adolescence. Even though clinical, histologic, and ultrastructural findings do not prove its etiology, some authors speculate that IEMP might be the result of a subclinical interface inflammatory process.

Although there is some similarity between erythema dyschromicum perstans and IEMP, the initial disease process occurs in the basal layer in the first case and was not present in the latter.

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Exogenous Ochronosis

12

Lynn Yuun Tirng Chiam

Abstract

Exogenous ochronosis is an uncommon dermatosis characterized as gray-brown or blue-black macules localized to the sites of application of topical agents. Although it is widely regarded as an uncommon complication of treatment with hydroquinone containing skin-lightening agents it may also be caused by topical substances such as phenol, resorcinol, and benzene.

Initially reported to be found almost exclusively in dark-skinned individuals and uncommon in other skin types, there are increasing reports of exogenous ochronosis affecting fairer individuals of skin types 3 and 4.

Keywords

Exogenous • Ochronosis • Hyperpigmented dermatosis • Hydroquinone • Macules • Topical agents

Introduction

- **No systemic complications**
- **Not inherited**
- **Gray-brown or blue-black darkening of skin**

Ochronosis is classified as endogenous and exogenous. Endogenous ochronosis or alkaptonuria is an autosomal recessive disease caused by the deficiency of the enzyme homogentisic acid oxidase. Exogenous ochronosis was first described in 1906 by Pick [1]. Exogenous ochronosis is characterized by coarsening and darkening of the skin. Histologically, exogenous ochronosis resembles endogenous ochronosis, but does not exhibit any systemic complications. Furthermore, exogenous ochronosis can be seen in any individual using a precipitating skin care product, and is not an inherited disorder. The association with hydroquinone use is strongest and was first reported in 1975 [2].

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Epidemiology

- **Affects all ethnic groups (African-American/Black, Asian, Hispanic, South East Asian)**
- **Low incidence**
- **Occurs after long-term usage of hydroquinone**

It has been recognized that exogenous ochronosis not only exists among darker skinned populations (skin phototypes V and VI) but affects all ethnic groups. There are increasing reports of ochronosis in fairer skinned Asians [3–7].

The worldwide incidence of exogenous ochronosis has been assumed to be low except in dark-skinned individuals from South Africa. With the recent reports from Asia, there is a likelihood of underreporting of the actual incidence of exogenous worldwide [3].

Exogenous ochronosis was thought to be caused by the chronic use of high concentrations of hydroquinone, lesions usually appearing after 3 years of usage. However, it has been described following the use of 2 % hydroquinone for less than 6 months [8–10]. Its appearance can mimic the original pigmentary alteration (e.g., melasma, post-inflammatory pigmentary alteration) and it appears to be a disease

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Table 12.1 Agents associated with exogenous ochronosis

- Hydroquinone
- Resorcinol
- Phenol
- Benzene

Table 12.2 Exogenous ochronosis is classified into three stages

Stage 1	Erythema and mild pigmentation
Stage 2	Hyperpigmentation, black colloid milium, and scanty atrophy
Stage 3	Papulo-nodular lesions with or without inflammation

occurring after the onset of adolescence, and more commonly in middle age.

Predisposing factors include usage of hydroquinone higher than 3 % and for more than 6 months, high Fitzpatrick skin phototype, lack of sun protection, and skin irritation (Table 12.1).

Clinical Presentation

- **Asymptomatic**
- **Classified according to severity**
- **Dermatoscopy may be useful**

Exogenous ochronosis presents as asymptomatic brown-gray or blue-black pigmentation on photoexposed areas or on contact sites. It mainly affects the face and neck [3, 4, 11, 12]. Exogenous ochronosis is classified into three stages [13] (Table 12.2):

Dermatoscopy has been reported to be a promising tool. Charlin et al. [10] described "bluish-gray amorphous areas obliterating the follicular structures." In contrast, melasma appears as accentuation of the normal pseudo-rete of the face. Other dermatoscopic features include "brown-gray globular, annular, and arciform structures [14]," "speckling [3]," and confetti-like leukoderma, which showed up as structureless areas on the skin [7].

Exogenous ochronosis is histologically confirmed by pigmentary incontinence, solar elastosis, presence of banana-shaped yellow-brown (ochre) fibers in the papillary dermis, and eventual collagen degeneration [10, 15, 16].

Differential diagnosis in adolescents includes post-inflammatory pigmentary alteration, cafe au lait macules, Becker's nevi, erythema dyschromicum perstans (which resembles dermoscopically), tinea versicolor, and melasma (especially older teenage females on oral contraceptives).

Pathogenesis

The exact pathogenesis of exogenous ochronosis is unclear. The most widely accepted theory is that of Penneys [17], which proposes that hydroquinone inhibits the local activity of the homogentisic acid oxidase, resulting in accumulation of homogentisic acid, which is polymerized, forming the ochronotic pigment and being deposited in the dermis.

Findlay et al. [2] theorized that with prolonged use of hydroquinone, melanocytes would overcome the bleaching effect of hydroquinone which would then pass down to the papillary dermis to be taken up by fibroblasts, resulting in attachment and polymerization of phenols in elastic fibers.

Another proposal [18] suggests that hydroquinone oxidizes into quinine, forming hydroxylated indoles similar to melanin precursors.

Treatment

- **Stop offending agent early**
- **No effective treatment**

There is currently no reported consistently effective treatment for exogenous ochronosis. Most importantly, creams containing hydroquinone should be identified and stopped. Topical treatment with retinoic acid, azelaic acid, and kojic acid and cryotherapy have been ineffective. Various modalities like dermabrasion and CO_2 laser [19, 20], Q-switched Ruby [21], Q-switched Alexandrite [15], and Q-switched Nd:YAG lasers have shown variable success.

Summary

Exogenous ochronosis should be considered in individuals in whom hydroquinone had been used for 6 months without any improvement. Recognition and early cessation of hydroquinone containing creams is the key as an erroneous diagnosis may lead to continuous drug application, leading to worsening of the pigmentation.

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13 Metabolic Hyperpigmentation: Carotenemia, Pernicious Anemia, Acromegaly, Addison's Disease, Diabetes mellitus, and Hemochromatosis

Luz Orozco-Covarrubias and Marimar Sáez-de-Ocariz

Abstract

Acquired diffuse hyperpigmentation in children secondary to metabolic disorders can be divided into nutritional diseases, endocrinological disorders, and metabolic causes. Although pigmentation is categorized as diffuse, it is often accentuated in some areas. Adequate approach of diffuse hyperpigmentation may lead to the early diagnosis of a specific disease. The initial and most prominent sign can be in the skin and thus the dermatologist is the first physician consulted.

Keywords

Pediatric • Diffuse hyperpigmentation • Metabolic hyperpigmentation

Nutritional Diseases

Carotenemia

Introduction

- **Carotenemia is yellow-orange skin pigmentation.**

Diet plays an important role in many skin disorders. The excess of specific nutrients such as carotenoids causes carotenemia.

Epidemiology

- **Pediatric carotenemia is a relatively common condition.**
- **More commonly seen in infants.**
- **All racial and ethnic populations are affected.**

It was described by Hess and Meyers in 1919 [1]. During World War I and II it was commonly seen because of food shortages. Currently in children the number of reported cases now is about the same more than 20 years ago [2, 3].

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Clinical Presentation

- **Yellow discoloration of the skin called carotenoderma.**
- **Artificial light makes the pigmentation particularly noticeable.**
- **Sclerae remain white.**

Carotenemia is a disorder of skin color secondary to the deposition of carotene in the subcutaneous fat and in the stratum corneum. The yellow-orange pigmentation of the skin appears first on the face most prominently on nasolabial folds and then becomes diffusely distributed, specially marked on palms (Fig. 13.1) and soles. Absence of pigmentation on mucous membranes excludes hyperbilirubinemia [4].

Pathogenesis

Humans do not synthesize carotene; carotene must be ingested. Fruit and vegetables are rich in carotene, even the green ones. Milk, egg, legumes, grains, etc., also contain significant levels of carotene.

One-third of ingested carotene is absorbed across the intestinal lumen. Some carotene is converted to vitamin A, but most is accumulated in the epidermis and in the subcutaneous fat. Excessive ingestion of carotene leads to carotenemia and it is the most common cause. However there are several diseases that have been associated with carotenemia such as hypothyroidism, diabetes mellitus, liver and kidney

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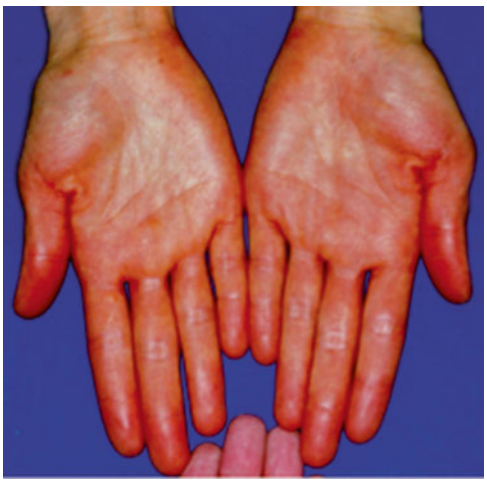

Fig. 13.1 Carotenemia. *Yellow-orange* discoloration on the palms as compared with that of a normal control

disease, anorexia nervosa, food faddism, and rare cases of inborn errors of carotene metabolism. Carotenemia occurs when carotene levels are greater than 250 mg/dL [2, 5].

Treatment

- **Reassure parents.**
- **Decrease the amount of carotene-rich food ingestion.**
- **Education about carotene-rich foods.**

There is no medical reason to reverse the carotene deposition in the skin. Discontinuation of excessive carotene intake typically returns the skin color to normal after 2–6 weeks. If other causes are suspected appropriate examination should be made.

Prognosis

Carotenemia is a benign condition.

Ongoing Research

Research on the biochemical and enzymatic pathways must provide insight into carotenemia particularly as it concerns infants with associated diseases.

Conclusion

Carotenemia affects infants of all races. In pediatric skin of color, yellow-orange discoloration is most noticeable on the palms. It is a frequent condition in children otherwise healthy. It disappears when dietary habits are changed. Parents must be informed.

Pernicious Anemia

Introduction

- **Hyperpigmentation of the skin is a clinical manifestation of vitamin B12 deficiency.**

Vitamin B12 plays an important role in DNA synthesis. Various clinical manifestations mainly neurological, hematologic, and cutaneous are found in patients with vitamin B12 deficiency [6].

Epidemiology

- **It is a major heath issue with prevalence around 20 % in industrialized nations.**
- **Breast-fed infants of strict vegetarian mothers are a risk group.**
- **All racial and ethnic populations are affected.**

Cook described pigmentation and vitamin B12 deficiency in 1944. Cutaneous manifestations are some of the lesser-known manifestations. These may be important to recognize to prevent irreversible complications [7, 8].

Clinical Presentation

- **Mucocutaneous lesions can be the clue for the early diagnosis.**
- **Unexplained and nonresolving skin lesions can be a red flag.**
- **Hyperpigmentation is more common in darker-skinned patients.**

Dermatological manifestations in patients with vitamin B12 deficiency include hyperpigmentation especially over the dorsum of the hands and feet with accentuation over the interphalangeal joints and terminal phalanges. Palmar creases, flexural areas, and pressure points are the most common affected areas (Fig. 13.2). The nails may have hyperpigmented streaks with pale nail beds. The association with pigmentation of oral mucosa (Fig. 13.3) is characteristic of vitamin B12 deficiency [8, 9]. Glossitis is the most common mucocutaneous manifestation followed by angular cheilitis. Hair changes manifest, as localized or diffuse depigmentation and vitiligo have been reported [9, 10].

Pathogenesis

Vitamin B12 cannot be synthesized in the human body and must be supplied in the diet. Serum levels less than 200 pg/mL mean definite deficiency. The primary source of vitamin B12 is derived from animal products such as meat, eggs, fish, and milk. The body stores large amounts of vitamin B12 so it takes 2–6 years to develop symptoms of deficiency [6, 8, 9].

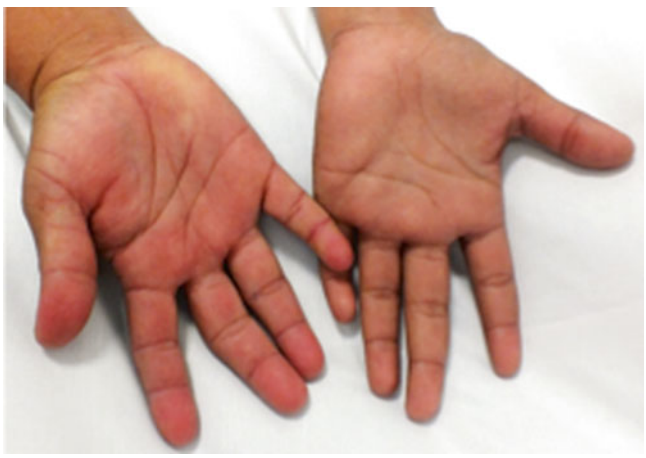

Fig. 13.2 Pernicious anemia. Palmar crease hyperpigmentation as compared with mother's palm

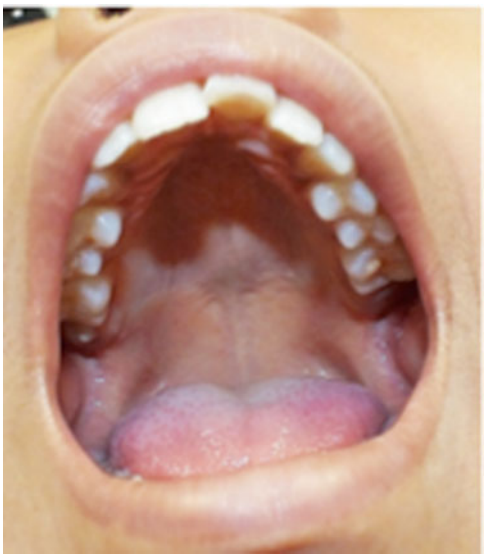

Fig. 13.3 Pernicious anemia. Pigmented lesions of oral mucosa

Causes of vitamin B12 deficiency are inadequate intake, malabsorption, and inborn errors of transport or metabolism. In children the must common cause is inadequate intake. The mechanism of hyperpigmentation is unknown; increased synthesis, defective transport, or a defect in distribution of melanin has been proposed [10].

Treatment

- **Initial replacement is through intramuscular injections.**
- **Children with normal absorption can be maintained on oral replacement.**
- **Treatment depends on treating the cause of deficiency besides supplementing with vitamin B12.**

The treatment of vitamin B12 deficiency must be started immediately because diagnosis of vitamin B12 deficiency is often overlooked in its early stages. Supplementation must be continued every month if symptoms persist.

Prognosis

Affection of the hematologic, gastrointestinal, and nervous systems can be avoided with an early diagnosis and adequate treatment. Cutaneous hyperpigmentation is completely reversible with treatment.

Ongoing Research

Research on causes of vitamin B12 deficiency is necessary to prevent complications.

Conclusion

Vitamin B12 deficiency causes a range of disorders and affects all age groups. Diagnosis is difficult because its presentation varies from being asymptomatic to affecting multiple organ systems. Unexplained skin lesions that do not respond to therapy can be an indication of vitamin B12 deficiency.

Endocrinological Disorders

Acromegaly

Introduction

- **Oversecretion of growth hormone.**
- **Overgrowth of acral bone and soft tissue.**

Growth hormone excess causes gigantism in children and adolescence, and acromegaly in adults.

Epidemiology

- **3–4 per million per year.**
- **Males and females are equally affected.**
- **About 20 % begins during adolescence.**

Acromegaly is a rare disorder. Virtually all patients have different tissue overgrowth with characteristic findings. Hyperpigmentation is more accentuated in patients with dark skin [11].

Clinical Presentation

- **Generalized increased pigmentation.**
- **Macrognathia.**
- **Enlargement of hands and feet.**

The most obvious cutaneous changes related with excess secretion of growth hormone is the thickening of the skin, an increase in the size and function of sweat and sebaceous glands, and an increase in hair follicles. The generalized increased pigmentation in approximately half of the children generally is moderate along with changes of the skin. Hyperpigmentation is particularly noticeable in pediatric skin of color where the skin is more thickened resulting in coarsening of the facial features. The nails become thickened and hardened. Acanthosis nigricans can be seen in many patients. The metabolic effects include diabetes, hyperlipidemia, and hypertension [11–14].

Pathogenesis

Excessive production of growth hormone is usually due to a benign pituitary adenoma. Growth hormone stimulates production of somatomedin by the liver and it is the increase in somatomedin levels that accounts for most of the alterations presented in acromegaly. The cause of hyperpigmentation is not understood since growth hormone has not a known function in melanin production [11].

Treatment

- **Surgical removal of the pituitary tumor.**
- **Residual disease requires somatostatin analogues.**
- **Growth hormone replacement therapy is usually required.**

Because clinical manifestations of acromegaly generally occur slowly, treatment is not corrective but rather preventive of further damage.

Prognosis

The skin changes can regress in days to weeks after lowering of growth hormone and somatomedin levels, although bony changes will persist.

Ongoing Research

Somatostatin analogues (e.g., octreotide) are increasingly being considered as potential primary therapy.

Conclusion

Acromegaly is a rare disorder secondary to growth hormone excess. The onset of symptoms is during adolescence in about 20 % of the cases. Approximately half of these children will develop diffuse hyperpigmentation.

Addison's Disease

Introduction

- **Generalized hyperpigmentation precedes other manifestations.**
- **Salt craving is characteristic.**

Addison's disease is an adrenal deficiency characterized by skin hyperpigmentation and salt wasting secondary to inadequate secretion of androgenic and corticosteroid hormones.

Epidemiology

- **Prevalence of 0.8–1.4 cases per 100,000 per year.**
- **Congenital adrenal hyperplasia is the most common cause in children.**
- **All races are affected.**

The age of the children at presentation depends on the cause of the Addison's disease. Adrenal hypoplasia and congenital adrenal hyperplasia usually present days after birth. Other causes can present at any age [15, 16].

Clinical Presentation

- **Diffuse bronze hyperpigmentation.**
- **Oral mucosa may be affected.**
- **Palmoplantar crease pigmentation.**

Hyperpigmentation is the most striking cutaneous sign in almost all cases of the chronic variety of adrenal hypofunction. Children present a generalized increased skin color accentuated in sun-exposed areas particularly in dark-skinned children (Fig. 13.4). Other areas with marked pigmentation are sites of trauma, around scars, and over areas of friction. Mucosal surfaces develop blue-brown macules (Fig. 13.5). Color changes on mucous membranes and palmoplantar creases are less marked in dark-skinned patients than in Caucasians. Darkened hair and pigmented bands in the nail plate are usually present [16–18].

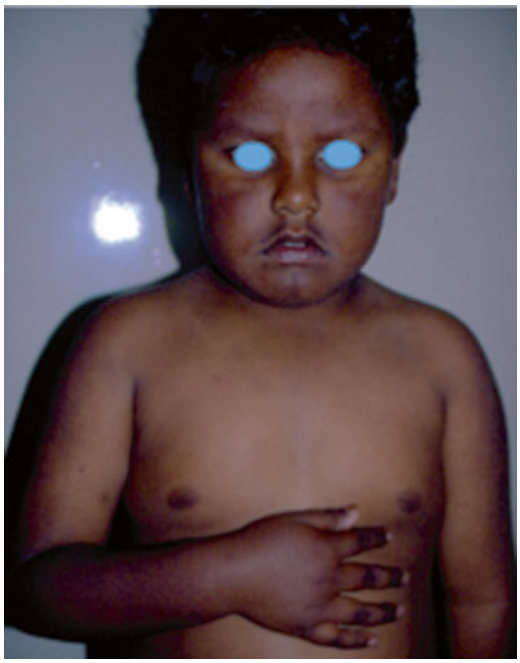

Fig. 13.4 Addison's disease. Generalized pigmentation. Note the accentuated hyperpigmentation in sun-exposed areas

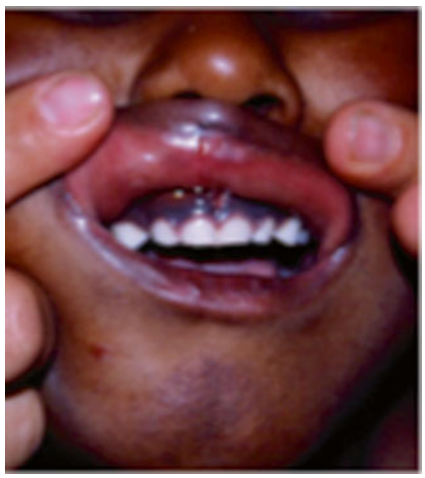

Fig. 13.5 Addison's disease. *Blue-brown* macules on mucosal surfaces

Pathogenesis

Reduced secretion of adrenocorticotropic hormone (ACTH), or failure of the adrenal cortex to respond to ACTH, results in Addison's disease in children. Most pediatric cases of Addison's disease are idiopathic. Hyperpigmentation is associated with elevated ACTH levels. The ability of ACTH to stimulate melanin production results in generalized hyperpigmentation [16–18].

Treatment

- **Glucocorticoid and mineralocorticoid replacement therapy.**
- **Additional therapy according to the cause.**
- **Children with idiopathic cause must be monitored for the development of other autoimmune diseases.**

Replacement therapy (e.g., hydrocortisone or fludrocortisone) is administered every day. Periods of stress (e.g., illness or surgery) will need an increased dose.

Prognosis

Adequate replacement therapy clears all the symptoms and signs. Hyperpigmentation decreases in all patients, and in some younger children, the skin color may return to normal.

Ongoing Research

Research on predisposing factors and that on the idiopathic group with a high incidence of circulating autoantibodies are required [19].

Conclusion

Adrenal insufficiency is a rare disease in children but still a cause of morbidity. Hyperpigmentation is characteristic of Addison's disease and suggests the clinical diagnosis.

Diabetes Mellitus

Introduction

- **Acanthosis nigricans is the most recognized cutaneous marker.**

Acanthosis nigricans (AN) is a dermatologic marker of hyperinsulinemia and it has been demonstrated that overweight and obese children with AN have a higher risk of early onset of type 2 diabetes [20].

Epidemiology

- **Most cases of AN are related to obesity and insulin resistance.**
- **AN is present in 10–20 % of school-age children and adolescents.**
- **Prevalence is higher in Hispanics.**

AN is common in the general population with predominance in females, but not all present insulin resistance. The percentage increases with being overweight. The rate of AN varies among different ethnic groups; the prevalence is lower in whites than in non-whites (0.5 % vs. 5–13 %) [21].

Clinical Presentation

- **Mild-to-severe flexural hyperpigmentation.**
- **Cutaneous thickening in the flexural areas.**
- **Symmetric distribution.**

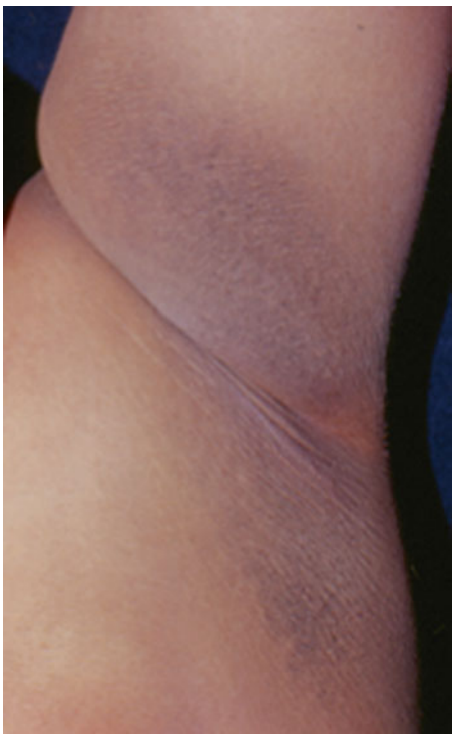

Fig. 13.6 Acanthosis nigricans. *Gray-black* pigmentation on axilla. Note the rugated hypertrophy and papillomatosis

AN affects both sexes before or after the puberty. Hyperpigmentation is the earliest sign and it may start as a dirty appearance. The brown to gray-black pigmentation usually localized to the neck, axilla, groin, abdominal folds, and any other flexural area is later accompanied by rugated hypertrophy and papillomatosis (Fig. 13.6). The extensor surfaces of the limbs and mucosal surfaces may be involved in severe cases. Intensity of pigmentation is correlated with the degree of insulin resistance, insulinemia, and obesity in children. The development of multiple skin tags is a common associated sign. It is necessary to be aware of associated findings even when obesity is one of the primary causes without insulin resistance [20, 22–24].

Pathogenesis

The classical histopathology of AN shows proliferation of keratinocytes and epidermal papillomatosis with no apparent abnormality of pigmentation. It is believed that high levels of insulin stimulate receptors for growth factors, but the specific mechanism is unknown. The main cause of the brown color of the cutaneous lesions is apparently the hyperkeratosis [23, 24].

Treatment

- **Therapeutic options for AN are ineffective.**
- **Therapy for the underlying cause may be benefit.**
- **Diagnosis of AN requires appropriate diagnostic approach.**

Keratolytics and bleaching agents are generally ineffective. Treatment of AN is determined by the underlying cause. Regular exercise in children can help to decrease insulin resistance. Improvement or resolution does occur with weight control in some overweight children.

Prognosis
AN should be considered an indicator of hyperinsulinemia, which is a known risk factor for type 2 diabetes.

Ongoing Research
Research for the role of different growth factors in the pathogenesis of AN continues. The possible genetic predisposition or increased sensitivity of the skin to hyperinsulinemia among different ethnic groups may be researched.

Conclusion
Cutaneous complications of AN are most commonly of cosmetic concern, but the main concern with these children is a diagnosis of a possible underlying disease.

Metabolic Causes

Hemochromatosis

Introduction
- **It is inherited as an autosomal-recessive defect.**
- **Clinical manifestations usually occur in homozygous individuals.**

Hereditary hemochromatosis is an autosomal-recessive disorder that disrupts the body's regulation of iron. It is a rare genetic disease in non-whites [25].

Epidemiology
- **It is a common genetic disease.**
- **About 10 % of individuals have one abnormal HFE gene.**
- **Men are much more affected than women.**

Phenotypically affected persons are homozygous for the HFE gene mutation C282y in about 85 %. Although hemochromatosis occurs mainly in men over the age of 40 years, there are reports of symptomatic children and adolescents [25, 26].

Clinical Presentation
- **Diffuse brown hyperpigmentation.**
- **Hyperpigmentation appears in patients with advanced disease.**
- **Hyperpigmentation can affect mucous membranes.**

Signs of hereditary hemochromatosis result from iron deposition in the liver and in other organs causing tissue damage. In the skin and mucous membranes bronze hyperpigmentation (Fig. 13.7) appears in about 70 %, and 20 % respectively even in children in patients with advanced disease. Besides hyperpigmentation the classic triad of hemochromatosis includes diabetes mellitus and hepatic cirrhosis. Children with disorders that require numerous transfusions may present secondary hemochromatosis. The pigmentation is usually generalized, but may be more pronounced in genitalia, scars, and sun-exposed areas especially in patients of skin color [26, 27].

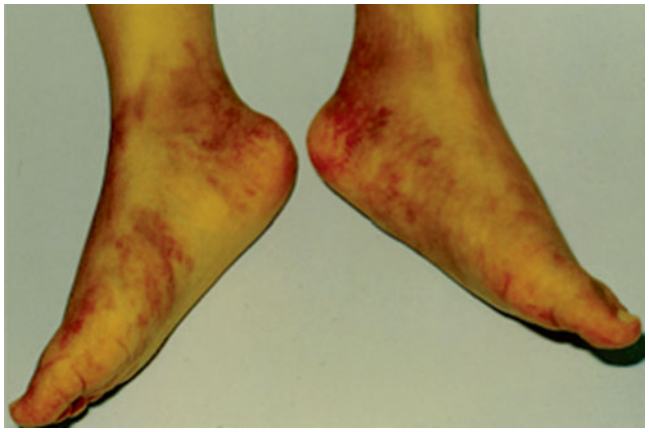

Fig. 13.7 Hemochromatosis. *Bronze* hyperpigmentation on both feet

Pathogenesis
Iron overload in hereditary hemochromatosis is associated with increase intestinal absorption of iron and iron status with deposition of excessive amounts of iron in different organs including the skin. Dietary interventions that modify iron intake may contribute to the management and possibly iron accumulation, but existing data are limited. Menstruation gives protection to women [28]. The pigment color of the skin is from melanin not iron deposition. How iron stimulates melanin production in the epidermis is not known but probably involves a reduction in the inhibitory effects of enzymes involved in melanogenesis [29].

Treatment
- **Therapeutic withdrawal of blood.**
- **Dietary modification is generally unnecessary.**
- **Universal screening is not recommended.**

Treatment of hereditary hemochromatosis requires phlebotomy. The frequency is guided by serial measurements of serum ferritin levels and transferrin saturation, with or without symptoms [25].

Prognosis
Detection of affected individuals either prior to or early during disease evolution may contribute to quality of life since iron toxicity can be attenuated or prevented [30]. Juvenile hemochromatosis is much more aggressive.

Ongoing Research

Besides the significant progress of the knowledge on iron metabolism many questions are still open particularly on special forms of iron overload, so research on iron metabolism is ongoing [31].

Conclusion

Hereditary hemochromatosis is an autosomal-recessive disease. Clinical manifestations can present in children as a result of iron deposition causing tissue damage. Skin bronzing is reversible once therapy is started.

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Part III

Hair Diseases in Children of Color

Genetic Hair Disorders

14

Carola Durán-McKinster

Abstract

The major types of hair shaft defects are associated with genodermatoses and syndromes. Clinically, hair shaft defects may cause an unusual appearance, or a fragile short and sparse hair. Light microscopy of hair shaft defects are classified by their morphology and it is an important tool for diagnosis. Hair shaft disorders are separated by hair fragility into those with or without increased fragility. Those with increased fragility include monilethrix, pili torti, trichorrhexis nodosa, trichorrhexis invaginata and trichoschisis. Hair shafts without increased fragility include pili annulati, loose anagen hair, wooly hair and uncombable hair. Advances in the genetic causes of the hair shaft defects are described in the different entities, which have allowed to understand the mechanisms of the defects and to elucidate normal and pathogenic pathways. In patients with hair shaft abnormalities as an isolated defect, the main problem is aesthetical. In contrast, when the hair shaft defects are associated with syndromes the prognosis will depend on the associations of each condition, especially when metabolic, neurologic or cardiac defects are present.

Keywords

Hair shaft defects • Monilethrix • Pili torti • Trichorrhexis nodosa • Trichoschisis • Trichorrhexis invaginata • Pili annulati • Loose anagen hair • Uncombable hair

Background/Introduction

Hair follicles are ectodermally derived and produce hairs that range in size from minute vellus hair to long, thick terminal hair. The hair shaft is composed of three layers: the medulla, the cortex and the cuticle. Evaluation of the hair bulb phases, e.g. anagen, catagen and telogen, is relevant to determine the different causes of alopecia. Anagen hairs have a pigmented and indented elongated root. In the scalp, anagen follicles usually grow from 2 to 7 years, while shorter hairs and vellus hairs have shorter growth periods. Anagen follicles are actively replicating and, therefore, are more susceptible to nutritional and metabolic deficiencies. Anagen hairs are difficult to detach in a pull test and therefore when present one should suspect a hair shaft disorder. Catagen phase occurs with cessation of pigment formation and migration of the dermal papillae and follicular unit towards more superficial layers of the dermis. Catagen hairs represent 1 % of the scalp hairs. Telogen hairs have short, club-shaped roots and pigment is lacking. With the formation of new anagen hair below the club, the developing follicle will replace the telogen hair leading to shedding 50–100 scalp hairs a day. Telogen hairs represent 6–10 % of all terminal scalp hair and are easy to detach with a pull test without pain. A pull test is performed using a gentle traction on the patient's hair; 4–6 or fewer hairs extracted is considered normal.

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Epidemiology/Demographics

- **Genetic hair shaft defects may present in almost all races.**
- **Epidemiology of the genetic hair shaft disorders varies according to the different syndromes.**

A retrospective review performed on an Asian pediatric population was recently reported. Hair samples from 119 patients in a 10-year period were examined microscopically; half of the studied patients had abnormalities in the hair and one-third (31 %) showed morphologic changes compatible with specific diagnoses of various genetic conditions including 25 cases of loose anagen hair syndrome, six cases of uncombable hair syndrome, two cases of Netherton syndrome, three cases of Menkes syndrome and one case of trichothiodystrophy [1].

Clinical Presentation

- **The recognition of the anatomic characteristics of normal hair is important when evaluating a patient with hair abnormalities.**
- **Light microscopy of the hair shaft and hair bulb is an important tool for the diagnosis of disorders affecting the hair.**
- **Hair shaft abnormalities are divided into those with or without increased fragility.**

Hair abnormalities can be seen in various genodermatoses and syndromes. One should suspect a hair shaft disorder if a patient presents with an abnormality or change in hair texture, color, appearance, manageability or ability to grow hair long. The initial evaluation includes a good history, physical examination and review of symptoms. A pull test determines whether there is hair breakage (increased fragility) by looking for broken hairs. An approach can be used to narrow the differential diagnosis in hair shaft disorders with and without fragility (Table 14.1). Light microscopy examination of the hair is necessary to evaluate the hair bulb and the microscopic structure of the hair shaft.

Clinically, patients with monilethrix usually present with diffuse alopecia with sparse, brittle short broken hairs on the entire scalp resulting from hair fragility over friction areas, predominantly the temporal and occipital regions. Other common findings are keratotic follicular papules at the nape of the head and keratosis pilaris, but a variable phenotypic expression and inheritance pattern are present. Hair rarely grows beyond 1–2 cm in length resulting in a stubbly appearance (Fig. 14.1a, b).

Table 14.1 Hair shaft disorders with increased fragility

Monilethrix
• The term monilethrix refers to hair shafts with elliptical nodes at regular intervals.
• The nodes have a diameter of normal hair and may be medullated, whereas the internodes are narrower and usually non-medullated, being the sites of fracture

Monilethrix is inherited as an autosomal dominant or autosomal recessive hair disorder with variable penetrance [2, 3]. Mutations are in the hair cortex keratins. The human keratin family comprises 54 members, 28 type I and 26 type II. Mutations causing autosomal dominant monilethrix have been found in the helix initiation and helix termination motifs of the type II hair keratins KRT81, KRT83, and KRT86 [4–6], while mutations in desmoglein 4 (DSG4) gene, which belongs to the desmosomal cadherin superfamily and is also expressed in the cortex of the hair follicle, are linked to recessive transmission [7].

Most monilethrix cases lack systemic involvement. Only isolated reports demonstrate association with congenital defects. A case report described atrophic alopecia associated with intractable scalp pruritus, diffuse keratosis pilaris, and bilateral posterior subcapsular cataracts and brachiocephaly, in a 9-year-old Turkish boy from consanguineous parents, suggesting an autosomal recessive trait [8]. Feng YG et al. reported a large Chinese pedigree with congenital monilethrix and hereditary unilateral external auditory canal atresia [9].

A diagnosis is elucidated by examining hairs by light microscopy observing the medullated nodes and non-medullated internodes in the hair shaft. Trichoscopy of scalp hair may reveal characteristic uniform elliptical nodes and intermittent constrictions along with variation in hair shaft diameter, presence of few vellus hairs and yellow dots. Dermoscopy of the keratotic follicular papules revealed multiple stubs of broken hair arising from them with a similar beaded appearance, suggesting a diagnosis of monilethrix [10].

There is no specific treatment that successfully cures the condition. A therapeutic trial with oral *N*-acetyl cysteine was attempted. There was slight improvement after 2 months of therapy. The hair density, however, did not show any further improvement subsequently [11]. Oral retinoids have been reported to obtain good clinical and cosmetic results while treatment was continued. In the past etretinate [12] and recently acitretin [13, 14] were reported to improve hair growth. However, clinical symptoms recurred after discontinuation and keratosis pilaris persisted. Topical 2 % minoxidil has been reported to increase the normal hair shaft without any side effects, after 1 year of treatment, and could be considered a good therapy [15].

Although there are no specific treatments prognosis is good.

Pili Torti

- **The term pili torti (PT) refers to a hair shaft which is flattened and twisted with an angle of 180°.**

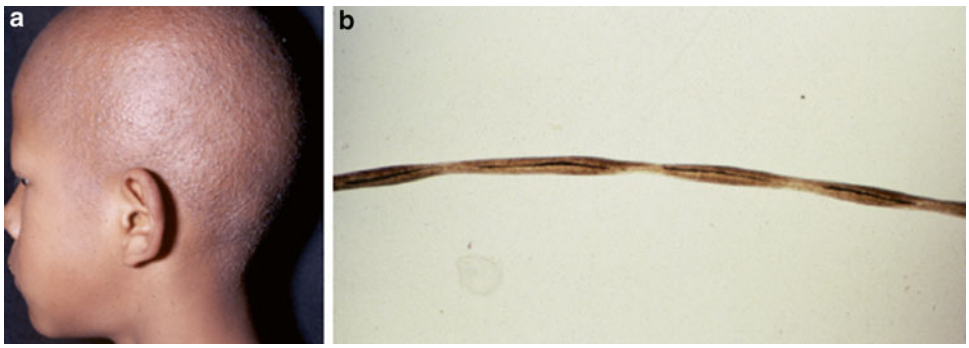

Fig. 14.1 (**a**) Monilethrix. Clinical appearance. (**b**). Hair shafts present elliptical nodes at regular intervals. ×20

- **Fracture occurs within the twist, which is the weakest point.**
- **Pili torti may occur as an inherited, isolated phenomenon or as a feature of different syndromes with neurological impairment, hearing loss or ectodermal dysplasias.**

Pili torti may occur as an inherited, isolated phenomenon with onset in the early months of life. The hair is usually fairer than expected and is spangled, dry and brittle. Alterations of the inner root sheath likely lead to the abnormal molding and twisting of the hair shaft on its own axis. Inheritance patterns can be autosomal dominant [16], autosomal recessive [17] or sporadic [18]. A late onset of pili torti has been described with the onset in childhood or after puberty. It is an autosomal dominant condition in white patients with black unruly, coarse, stiff hair and non-progressive mental deficiency [19]. Other inherited entities may present pili torti and include Menkes syndrome, Björnstad syndrome, Crandall syndrome and ectodermal dysplasia.

Menkes kinky hair syndrome, also known as trichopoliodystrophy, is a rare X-linked recessive, progressive neurodegenerative with connective tissue manifestations. It is clinically characterized by progressive psychomotor impairment, treatment-refractory seizures and hair shaft abnormalities [20], most commonly PT, but other defects, such as trichorrhexis nodosa (TN), have been described. The condition is related to a mutation in a copper-transporting gene located on chromosome Xq13.3 resulting in a disorder caused by deficiency or dysfunction of a copper-transporting ATPase, ATP7A [21]. Four types of Menkes disease can be distinguished. The two extremes forms, the severe classical form and the mildest, called occipital horn syndrome (OHS), affect >90 % of patients. Moderate and mild forms likely represent variant of MD and OHS. The infants appear normal at birth and then typically develop neurologic deterioration, lethargy and a loss of milestones in the second or third months of age. Skin and hair hypopigmentation and bone and connective tissue alterations with soft skin and joint laxity are present. There is microcephaly and the hair shaft does not grow long and is easily broken. Light microscopy is an important clue for the early suspicion of Menkes syndrome. Flattened hair is twisted 180° along its axis intermingled with normal hair (Fig. 14.2). The diagnosis can be confirmed by a low plasma level of copper and ceruloplasmin. If untreated, most patients die within the first year of life. Longer-term survivors are reported as a result of early treatment with parenteral administration of copper in the neonatal period. It may prevent neurological deterioration but does not improve the non-neurological features such as hair or connective tissues laxity [22].

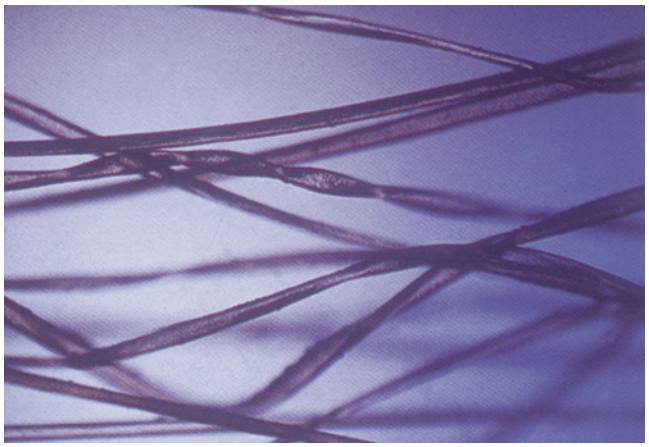

Fig. 14.2 Pili torti. Hair is twisted 180° along its axis intermingled with normal hair. ×20

Björnstad and Crandall Syndromes

Pili torti and hearing loss

In 1965, Björnstad described eight patients with pili torti and hearing loss [23]. The combination of these two findings was later coined Björnstad's syndrome. Patients develop hair loss in the first 2 years of life, while the hearing deficit may become evident in the first 3–4 years of age. Only 39 cases of Björnstad syndrome have been reported in the English literature and only two cases have been reported in Japan [24].

Both autosomal and recessive inheritance patterns have been described and mapped to the gene locus 2q34–q36 [25].

Al-Owain et al. described a novel phenotype in a series of nine Saudi Arabian patients from four consanguineous families three of which were related. They identified a causative mutation in the BCS1L gene [26].

Crandall syndrome is similar to Björnstad syndrome but presents with hypogonadism [27]. Most cases are autosomal recessive.

Mental retardation is rarely associated in both syndromes.

Trichorrhexis Nodosa

- **The term TN refers to the light microscopic appearance of a fracture associated with swelling of cortical cells.**
- **The hair is very fragile and it breaks readily with trauma or spontaneously.**

TN may occur alone but has been reported in certain genodermatoses and metabolic disorders.

In congenital TN, inherited as an autosomal dominant trait, the hair is usually normal at birth but is replaced within a few months with abnormal, fragile hair. The condition tends to improve with age.

In two main metabolic inborn errors of the urea cycle, argininosuccinic aciduria and citrullinemia, TN can occur. TN occurs in approximately 50 % of cases of the neonatal form of argininosuccinic aciduria while in citrullinemia may present TN, atrophic hair bulbs, and/or pili torti. Clinically, manifestations are similar in both conditions; symptoms include lethargy, seizures, respiratory distress and development delay. Hair is usually normal at birth, with later development of dry, dull hair and TN. The light microscopic appearance of TN is a fracture associated with swelling of cortical cells and splaying them out from the main body of the hair shaft resembling the end of a brush (Fig. 14.3).

Fig. 14.3 Trichorrhexis nodosa. Swelling of cortical cells causes a fracture resembling the end of a brush. ×40

Fig. 14.4 Microscopic appearance of a sharp transverse fracture characteristic of trichoschisis. ×40

The condition reverts to normal with dietary treatment of the metabolic condition, but it recurs quickly if the diet is abandoned [28].

Trichoschisis

- **The term refers to the light microscopic appearance of a sharp transverse fracture of the hair shaft (Fig. 14.4).**
- **Under polarized light, the characteristic "tiger tail" pattern alternating bright and dark diagonal bands are observed.**
- **Trichoschisis is a marker for a neuroectodermal disorder named trichothiodystrophy with brittle hair and low sulfur content of hair.**

Trichothiodystrophy (TTD) is a heterogeneous rare group of autosomal recessive disorders of DNA repair unified by the presence of sulfur-deficient brittle hair. It is caused by a mutation of a regulatory gene involved in the transcription of DNA. There is a wide variety of phenotypes, from brittle hair only to severe intellectual impairment and developmental delay (Fig. 14.5).

Eight subgroups have been categorized by Itin et al. [29] and include BIDS (*b*rittle hair, *i*ntellectual impairment, *d*ecreased fertility, and *s*hort stature), IBIDS (BIDS + *i*chthyosis), PIBIDS (BIDS + *p*hotosensitivity), SIBIDS (oto*s*clerosis + IBIDS), ONMR (*o*nychotrichodysplasia, chronic *n*eutropenia, and *m*ental *r*etardation), and Sabinas, Pollitt, and Marinesco–Sjögren syndromes [30]. Individuals with TTD may present with a collodion baby phenotype and intrauterine growth retardation can occur.

In TTD, 95 % of photosensitivity patients have abnormalities in nucleotide excision repair (NER) and can be assigned to the xeroderma pigmentosum (XP) complement group D (XPD) [29]. Non-photosensitivity TTD patients represent a genetically heterogeneous disorder. Mutations in chromosome 7p14 have been identified in two types of patients with Amish brittle-hair syndrome and non-photosensitivity TTD with mental retardation and/or decreased fertility [31].

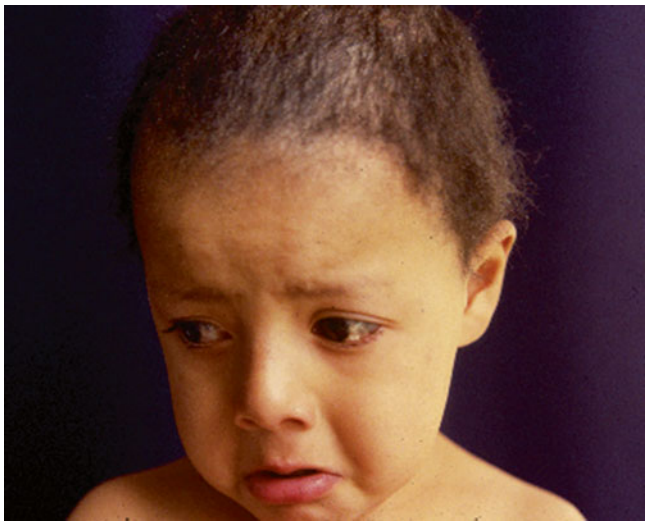

Fig. 14.5 Clinical aspect of a patient with trichothiodystrophy and mental retardation with brittle short hair

The clinical appearance is a short, brittle, disordered sparse hair. This may be absent at birth and is not fully developed until 3 months of age [32]. On light microscopy, the hair has an irregular outline and a flattened shaft in which twists occur like a folded ribbon. Two types of fractures are seen—trichoschisis and an atypical trichorrhexis nodosa (less splaying out of the cortical cells). Under polarized light the typical "tiger tail" pattern confirms the diagnosis. The low cystine (sulfur) content of hair is postulated to account for cuticular and cortical weakness, provoking the fracture. A study reveals an inverse correlation between sulfur content and percent of hairs with shaft abnormalities (trichoschisis, trichorrhexis nodosa, or ribbon/twist), but there was no association between clinical disease severity and percent of abnormal hairs [33].

Diagnosis. Is made by visualization of the "tiger tail" banding seen in all hairs with polarizing microscopy providing a reliable diagnostic test. Scanning electron microscopy shows a flattened shaft with irregular ridging and disordered reduced, or absent cuticle scan pattern.

Trichorrhexis Invaginata

- **The term refers to a distal hair shaft invaginating into the proximal hair shaft ("bamboo hair").**
- **Trichorrhexis invaginata (TI) is the characteristic hair abnormality of Netherton syndrome.**

Netherton syndrome (NS) is a severe autosomal recessive skin disorder characterized by congenital ichthyosiform erythroderma, TI, and atopic manifestations with an elevated IgE level [34]. Recently, pathogenic mutations were identified in serine protease inhibitor Kazal-type 5 (SPINK5) [35], the gene that encodes lympho-epithelial Kazal-type related inhibitor (LEKTI), a type of serine protease inhibitor involved in the regulation of skin barrier formation and immunity. The major neonatal complication is the hypernatremic dehydration and staph skin infections complicated by neurologic signs.

Although the severity varies considerably, the clinical and microscopic findings are present from birth with a large variability in phenotypic expression. Most patients present a congenital generalized exfoliative erythroderma which can last up to 2 years followed by an ichthyosiform eruption with polycyclic erythematous plaques with fine double-edged scaling, named ichthyosis linearis circumflexa (Fig. 14.6).

The presence of trichorrhexis invaginata is necessary to make the diagnosis of NS, but identification can be difficult because this defect is variable in time and localization. In the severely affected neonate, the hair may be extremely sparse or even absent. When hair is present it is fragile, short and dull. The changes may affect eyebrows, eyelashes and general body hair also. The examination of eyebrow hairs is especially beneficial for patients with the hair scalp so minimally affected that the diagnosis cannot be made from sampling from this area [36].

Microscopy of scalp hair may show a typical and complete "bamboo hair," but sometimes only an invaginated hair shaft is observed ("golf tee hair") due to the expanded proximal end of an invaginated node after a break occurred [37]. Trichoscopy in patients with very dark skin can be difficult, due to a lack of contrast with the background skin. Clipping hair and placement on a white background can aid in visualization of the bamboo hair deformity [38].

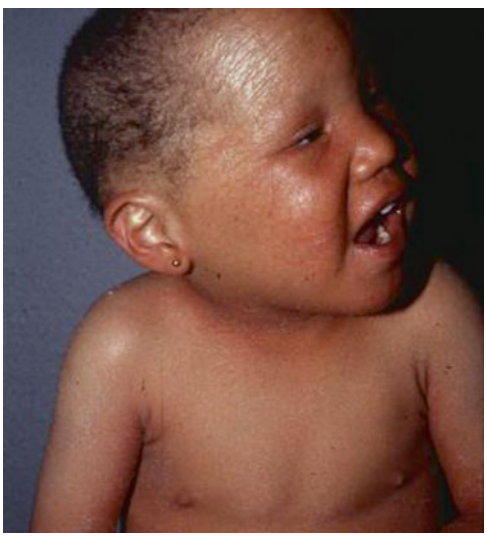

Fig. 14.6 Netherton syndrome in a patient with congenital ichthyosiform erythroderma. Hair is sparse as well as eyebrows and eyelashes. Courtesy Prof. R. Ruiz-Maldonado

Because of severe complications frequently occurring in the neonatal period, NS prognosis can be poor in infancy. Various therapeutic options have been used in NS with variable success. There have been conflicting reports of the usefulness of tacrolimus in NS patients, with systemic absorption being the main adverse outcome. Saif et al. reported four Saudi siblings with NS who were treated with topical tacrolimus and pimecrolimus with good control of their skin disease without any toxic effect [39]. However, NS management is still problematic due to the lack of specific treatment and unmet needs.

Hair Shaft Disorders Without Increased Fragility

Pili Annulati

- **The term refers to a pattern of alternating bright and dark bands of the hair, observed as shiny beads seen along the hair shaft.**
- **This pattern is due to the periodic occurrence of air-filled cavities along the hair cortex.**

Pili annulati (PA) is a rare autosomal dominant hair disorder clinically characterized by a pattern of alternating bright and dark bands of the hair, the bright bands appearing dark if observed by transmitted light. This pattern is due to the periodic occurrence of air-filled cavities along the hair cortex which scatter and reflect the light while precluding its transmission.

Most cases have been reported in Caucasian individuals, with only one case reported in an African-American patient [40]. PA has been mapped to chromosome 12q24.32–24.33 [41].

The condition is benign and has no associated systemic diseases or skin disorders.

Concomitant manifestation of pili annulati with alopecia areata has been reported [42] although a direct association between pili annulati and alopecia areata seems unlikely [43].

PA is accepted to belong to the classification of hair shaft abnormalities without fragility, although a 14-year-old Turkish girl with fair skin and dark hair was diagnosed as PA with fragility of the hair demonstrated by weathering features in electron microscopic examinations [44].

Diagnosis of PA is made by transmitted light microscopy of the hair shaft which reveals periodic dark bands in the hair shaft (Fig. 14.5). Treatment is not necessary.

Loose Anagen Hair

- **The term loose anagen hair refers to anagen hairs with misshapen pigmented hair bulbs, absent inner and outer root sheaths, a ruffled appearance of cuticle and a longitudinal groove parallel to the long axis of the hair shaft (Fig. 14.7).**

Fig. 14.7 Loose Anagen hair. Characteristic pigmented distorted bulb, absence of inner and outer root sheaths, and ruffled appearance of cuticle. ×40

The development of loose anagen hair (LAH) [45] may be sporadic, may occur in association with developmental or acquired conditions (e.g. alopecia areata, Noonan syndrome and ectodermal dysplasia) or, less commonly, may be a familial disorder.

LAH is characterized by the ability to easily and painlessly extract unsheathed anagen hairs from the scalp with gentle traction. The hair is sparse, and main complaints are patchy or diffuse alopecia and/or slow growth of hair. Usually the hairs are not fragile and do not have areas of breakage. The condition is of cosmetic concern and does not affect the general health.

Price et al. described in the 1980s loose anagen hair syndrome (LAHS) that was considered a sporadic condition found predominantly in blonde hair females [46]. Since then, there have been multiple reports of LAHS occurring in families and males, with equal sex ratio [47]. It is an autosomal dominant hair disorder with incomplete penetrance that primarily affects children but is occasionally seen in adults.

All reports in the English literature described LAHS mainly in white patients with blond hair, but the condition may present in dark-skinned children as well. Black or African-American children with loose anagen syndrome require a fungal culture to exclude tinea capitis [48, 49].

For diagnosis is made by performing a hair pull test and a trichogram to confirm the characteristic misshapen anagen bulbs devoid of sheaths, a ruffled appearance of cuticle and the longitudinal groove parallel to the long axis of the hair shaft [50]. The hairs are sometimes referred to as looking like "rumpled socks". Although the mere presence of LA hairs on a hair pull test is thus not specific for LAHS in children, the number per hair pull may have diagnostic significance. Most children improved spontaneously within a few years; however, hair shedding continued.

Uncombable Hair

- **It is a relatively rare anomaly of the hair shaft, with less than 100 cases reported.**
- **The hair shaft has a triangular configuration and a well-defined longitudinal depression.**
- **Diagnosis is suspected clinically and confirmed by scanning electron microscopy.**

Uncombable hair syndrome (UHS) (also known as pili trianguli en canaliculi or spun-glass hair) was first described by Dupre et al. in 1973 [51]. Both inherited (autosomal dominant and recessive with variable levels of penetrance) and sporadic forms of UHS have been described [52–54], both being characterized by disorganized, unruly hair pattern that is impossible to comb flat. The hair is normal in quantity and sometimes also in length. Most individuals are affected early in childhood and the hair takes on a spun-glass appearance with the hair becoming dry, curly, glossy, lighter in color, and progressively uncombable. Only the scalp hair is affected.

Under the light microscope the hairs may appear normal. Cross-sectional microscopy shows a triangular shape of the hair follicle. Scanning electron microscopy shows a characteristic triangular or heart-shaped hair shaft with a longitudinal groove along the entire length of the hair [55].

The condition is usually isolated; however, reports of uncombable hair and enamel defects of the teeth and nail abnormalities that classify for a subtype of ectodermal dysplasia have been associated with the syndrome [56].

As a rule, the condition becomes obvious during the first years of life. In most cases the hair is grossly abnormal in infancy and early childhood. There is no definitive treatment and most cases improve with the onset of puberty.

Wooly Hair

- **Woolly hair by definition occurs only in persons of non-African ancestry**
- **It is characterized by a tight, curly hair which differs from other family members**
- **Wooly hair (WH) is important because there are many associations**

WH is usually abnormal from birth. The hair is not fragile and the pathogenesis is unclear and varies from case to case.

Three main groups have been described. Two are diffuse and inherited, one autosomal recessive and one autosomal dominant. The third group is localized and sporadic, the woolly hair nevus.

Hairs are tightly curled, with an average curl diameter of 0.5 cm and can make twists along its own axis. By electron microscopy, the hairs are flat and oval or irregular on transverse sections; longitudinal and transverse grooves are present in the proximal part of the hair shaft, resulting in irregular contour of the hair. Axial torsions are occasional and different from true Pili torti [57].

Autosomal recessive woolly hair (ARWH)/hypotrichosis is a hereditary hair disorder which is characterized by tightly curled hair and is associated with sparse hair. ARWH can be caused by mutations in the P2RY5 or lipase H (LIPH) gene. Disruption of either gene results in phenotypes with features of both woolly hair (WH) and hypotrichosis. This mutation has been described in families from Pakistan and Guyana [58].

Hereditary dominant WH is observed from birth or in the first few months of life. Hair is fine, soft and frizzy woolly hair with generalized hypotrichosis. It usually occurs alone, but has been reported with ocular problems, or atrophic follicular keratosis [57].

WH may be associated with cardiac abnormalities: Naxos disease and Carvajal syndrome, both inherited as autosomal recessive conditions.

Naxos disease presents the association of arrhythmogenic right ventricular cardiomyopathy (ARVC) with woolly hair and palmoplantar keratoderma [58]. Mutations in genes encoding the cell adhesion proteins plakoglobin, a key component of desmosomal junction and found in heart, skin, and hair, were identified to underlie this syndrome and mapped to chromosome 17q21 [59]. Carvajal syndrome was described with a particular mutation in desmoplakin in Ecuadorian families, and results in a variant of Naxos disease with predominantly left ventricular involvement, early morbidity and clinical overlapping with dilated cardiomyopathy [60].

Woolly hair nevus (WHN) affects a localized area on the scalp. It may be present within the first 2 years of life, although onset in adolescence has been reported. It has been associated with epidermal nevus syndrome, with epidermal nevi and with white sponge nevus [61, 62]. WHN can follow Blaschko lines, suggesting that it may be a mosaic disorder.

Prognosis

In patients with hair shaft abnormalities as an isolated defect, the main problem is aesthetical. In contrast, when the hair shaft defects are associated with syndromes the prognosis will depend on the associations of each condition, especially when metabolic, neurologic or cardiac defects are present.

Ongoing Research

Although genetic hair shaft abnormalities are rare conditions in pediatric dermatology practice, recent advances in molecular genetics have led to the identification of many genes expressed in the hair follicle.

Conclusion

The recognition of the nomenclature and characteristics for the specific hair shaft defects is important when evaluating a patient with hair abnormalities and an important tool for the diagnosis. The major types of hair shaft defects are associated with syndromes. Many of the genes causing hair shaft defects have been described, allowing better understanding of the underlying pathophysiology. Clinically, hair shaft defects may cause an unusual appearance, or a fragile short and sparse hair.

Hair shaft disorders are separated into those with or without increased fragility. A pull test is performed using a gentle traction on the patient's hair, where 4–6 or fewer hairs extracted is considered normal. With the use of light microscopy, defects may be classified by the hair shaft morphology. Those with increased fragility include monilethrix, pili torti, trichorrhexis nodosa, trichorrhexis invaginata and trichoschisis. Hair shafts without increased fragility include pili annulati, loose anagen hair, wooly hair and uncombable hair.

Advances in the causes of hair shaft disorders in the fields of molecular biology, biochemistry and genetics are necessary to elucidate mechanisms of these defects, and to find successful therapies.

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Traction Alopecia

15

Sejal K. Shah

Abstract

Traction alopecia (TA) is a type of traumatic hair loss caused by excessive pulling of the hair. It is commonly due to cultural, social, or cosmetic hairstyling practices. Although initially reversible, it may progress to a permanent hair loss if the causative traction persists. Therefore, early diagnosis and management are central to preventing irreversible hair loss.

Keywords

Traction alopecia • Traumatic alopecia • Corn-row alopecia • Chignon alopecia • Fringe sign • Follicular degeneration syndrome • Permanent alopecia

Traction alopecia (TA) is a common type of hair loss caused by trauma to the hair. Since first described in 1907 among females from Greenland [1], it has been reported in various racial groups and attributed to that group's particular hairstyling practice.

Epidemiology/Demographics

- **Females are more commonly affected than males**
- **TA has been reported in various racial groups and occurs in both adults and children**
- **In the United States, it is largely seen in skin of color populations**

Racial groups in which TA has been reported
African/African-American
Hispanic
Indian
Caucasian
Japanese
South Korean

Although TA occurs more commonly in females, it has been reported in males [2–4]. It is found in both the adult and pediatric population. In the United States, it is primarily seen in individuals of African and Hispanic descent due to hairstyling practices, such as weaving, tight ponytails, tight braiding, "corn-rowing", and hair straightening that cause excess tension on the hair. In 2007, Khumalo et al. [5] conducted a population-based study looking at the relationship between hairstyling practices and scalp diseases in 1,042 South African school-aged children, 574 (55 %) girls and 467 (45 %) boys. All cases of TA occurred only in girls, with a prevalence of 17.1 % in girls and an overall prevalence of 9.4 %. Of the girls with TA, 8 were noted to have natural hair and 90 had relaxed hair on exam. Two hundred and fifty-nine girls had a prior history of braids: 170 with braids on natural hair, 84 with braids on relaxed hair, and 5 with dreadlocks. The prevalence of TA in these groups was 22.9 %, 32.1 %, and 0 %, respectively. The difference between the first two groups was not significant. The authors did note a significant difference ($p<0.0001$) in the prevalence of TA between the

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girls with natural hair on exam and a history of braids on natural hair: 5.2 % versus 22.9 %. However, use of relaxers confounded this difference. Thus, the authors concluded that TA is significantly associated with relaxer use, but the correlation with a history of braids is unclear [5].

TA has also been associated with hair rollers, backcombing, nylon brushes, tight scarves around the scalp, and headbands [6–11]. Eyelash extensions have been associated with TA of the eyelashes, which may result in permanent loss [12]. Of note, traction has been implicated in the pathogenesis of follicular degeneration syndrome as traction can produce irritation or injury that results in follicular degeneration [13, 14].

Clinical Presentation

- **Chronic TA is the more common form of TA.**
- **The "fringe sign" defined as retained hairs along the frontal and/or temporal hairline, is a useful clinical marker.**
- **TA may be marginal (along the hairline), nonmarginal, or both depending on the inciting hairstyle.**

TA occurs as either acute or chronic hair loss. Acute TA is relatively uncommon and is a result of accidental or intentional forceful removal of the hair for which there is a clear history, such as a motor vehicle accident [11, 15]. Chronic TA is more commonly seen and has a gradual and predictable course. It is typically symmetrical; the exact pattern depends on the causative hairstyle. A thin strip of hair is often preserved at the distal edge due to hairs that are too short to be pulled back; this is known as the "fringe sign" [16]. Other clinical features that may be present include follicular and perifollicular papules, pustules, erythema, scale, broken hair shafts, and peripilar keratin casts, which are 3- to 7-mm yellow-white mobile cylinders on the hair shaft [1, 17–19]. Permanent scarring hair loss can occur as a result of prolonged traction.

TA can occur in a marginal or a nonmarginal pattern. In marginal TA, hair loss occurs along the margins of the scalp, characteristically at the temporal scalp and extending forward to involve the frontal and periauricular scalp (Fig. 15.1) [20, 21]. The temporal scalp is commonly involved due to constant contraction of facial muscles superimposed on the tension caused by tight hairstyles (e.g., braids or ponytails) [21, 22]. An ophiasiform pattern of hair loss can also occur [23, 24]. Marginal TA is commonly noted in African-American females.

Nonmarginal TA does not occur at the margins of the scalp. Chignon alopecia is a type of nonmarginal TA localized to the occipital scalp where the bun rests [25]. In "cornrow alopecia" severe hair loss occurs adjacent to where the hair is parted [21, 26]. Hair extensions or weaving may result in a nonmarginal TA in the crown area where the scalp hair and the extensions are attached [3, 11, 27]. Other potential causes include nurse caps that are pinned to the scalp and hair rollers [6, 28]. Marginal and nonmarginal TA are not mutually exclusive and can occur together [20].

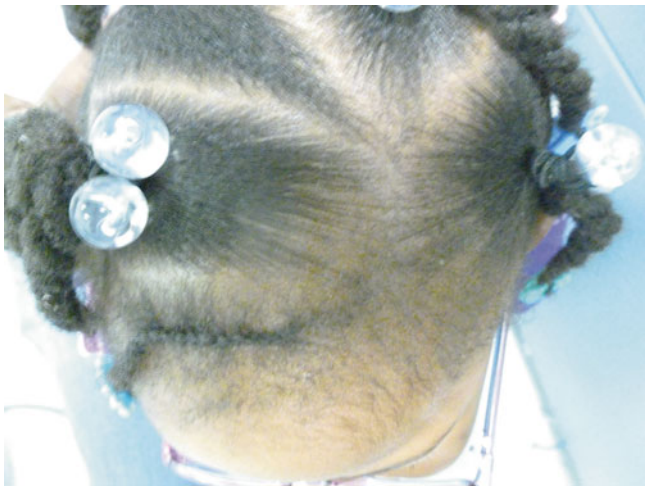

Fig. 15.1 Notable tension from hairstyling is resulting in follicular prominence and hair loss along the hairline and parts in this 2-year-old African-American female (photo courtesy of Nanette B. Silverberg, MD)

The diagnosis of TA is based on a thorough history and physical exam, including a detailed history of hair care and styling practices. Blood tests are usually unnecessary. However, a biopsy may be helpful if the clinical presentation is questionable. In early TA, the histologic findings are similar to those found in trichotillomania but usually subtler. The total hair count is normal to slightly decreased; follicular damage is not prominent; and trichomalacia and pigment casts are rarely seen [29]. Subacute perifollicular inflammation with occasional parakeratosis may be present [21]. Traction on the hairs triggers a premature conversion of hairs into the telogen stage resulting in a reduced anagen to telogen ratio [11]. Advanced TA is characterized by reduced or absent hair follicles and perifollicular fibrosis that extends to the subcutaneous fat resulting in vertical tracts of scarring [25, 28]. In both early and late disease, the number of vellus hairs remains normal [29]. The epidermis may be unaffected or show slight hyperkeratosis with irregular acanthosis. Blood vessels and eccrine glands remain normal, but sebaceous glands may be decreased in density [21, 30]. Inflammation is typically not a prominent feature [11].

Differential Diagnosis

Other forms of alopecia, both scarring and nonscarring, are in the differential diagnoses. Alopecia areata is the most common misdiagnosis [24, 25]. Other differential diagnoses include trichotillomania, occipital pressure alopecia, circumscribed scleroderma, tinea capitis, and loose anagen syndrome. In advanced stages once there is scarring and permanent hair loss, TA can resemble any form of end-stage scarring alopecia. As individuals with androgenetic alopecia

(AGA) are susceptible to developing TA, this diagnosis should always be considered [25, 31].

Treatment

- **Reducing or discontinuing traumatic hair care practices is central to any treatment strategy.**
- **Antibiotics, steroids, and minoxidil may be helpful, especially in early stages.**
- **In advanced cases, surgical interventions and camouflaging techniques are necessary.**

Successful treatment and prevention of permanent alopecia depend on early diagnosis. First and foremost, the discontinuation or reduction of traumatic hair care practices that exert excess traction on the hair should be advised. Individuals of African descent should be encouraged to try natural hairstyles. Topical antibiotics (e.g., clindamycin) or oral antibiotics (e.g., minocycline) may be needed if a coexistent folliculitis is present [21]. Steroids, topical (e.g., fluocinolone) or intralesional (e.g., kenalog 5 mg/cc), or minoxidil (2 %) may be helpful [11, 32–34]. In late-stage TA, surgical treatments and camouflaging techniques, such as hair pieces and wigs, may be the only viable alternatives. The surgical options include simple excision of the area of permanent alopecia, excision and scalp reduction with the implantation of an extender, excision followed by coverage with scalp flaps with or without the use of tissue expanders, and hair transplantation. Children can undergo surgical treatments for TA but often require general anesthesia for these procedures [35].

Prognosis

If recognized early and the offending hair care practices are stopped before scarring occurs, TA is reversible. However, once scarring occurs due to prolonged traction, the follicles have been destroyed and the hair cannot recover.

Conclusion

TA is a common form of hair loss that results from excess tensile forces applied to the hair. Although it is potentially reversible, it can progress to irreversible hair loss if left unaddressed. Therefore, early diagnosis is crucial. Management primarily involves minimizing traumatic hair care practices. Additional medical treatments may be helpful in some cases. Once the alopecia is permanent, treatment options are limited to surgical treatments and camouflaging techniques.

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Acne Keloidalis Nuchae

16

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Abstract

Acne keloidalis nuchae is an acneiform condition with keloidal scarring that is noted in the nuchal area in adolescent and adult males. The disease primarily affects boys of African descent including Blacks, African Americans, Africans, and Afro-Caribbeans, but can be noted in any racial or ethnic grouping. Trauma including shaving of the nuchal scalp, helmets, and friction (e.g., from collars rubbing) can all contribute to disease. Therapy begins with limitation of shaven hairstyles, reduction in friction from clothing and gear, topical and/or oral acne medications, and cosmetic therapies including intralesional corticosteroid therapy, laser hair removal, and excision in severe cases. Disease rarely reaches the severity requiring laser or excision in childhood and the aim of therapeutic interventions is in part reduction of lifetime disease severity through prevention and early disease intervention.

Keywords

Acne keloidalis nuchae • Keloids • Shaving

Introduction

Acne keloidalis nuchae (AKN) was initially described by Kaposi in Germany in 1869 as *dermatitis papillaris capillitii* [1]. Also known as Folliculitis Keloidalis, AKN is a chronic inflammatory disease of the hair follicle that most commonly affects Black, African, or African-American males aged 14–25 [2].

The incidence of AKN is 0.7–9 % of dermatology patients and appears to be increasing with time [3]. Clinically, AKN is characterized by follicular-based papules and pustules over the posterior and nuchal scalp, as well as the nape of the neck (Fig. 16.1). Keloidal scarring can occur as a result of the illness.

This inflammatory disorder of the follicle occurs in visible areas, and therefore tends to have significant negative psychological effects. Intrusive thoughts about the disease, impaired sexual relationships, and pain are some of the comorbidities of the disease. The comorbidities, the high rate of occurrence, and the increasing incidence all establish AKN as a significant and debilitating skin disease.

Epidemiology/Demographics

- **AKN is a disease of young African-American males, aged 14–25 years**
- **Closely shaven hairstyles and friction from collars and/or sports equipment promote disease development**
- **The disease is noted in males of African origin worldwide**

Acne Keloidalis nuchae is a disease primarily of African-American males aged 14–25 years, but Hispanic teenage

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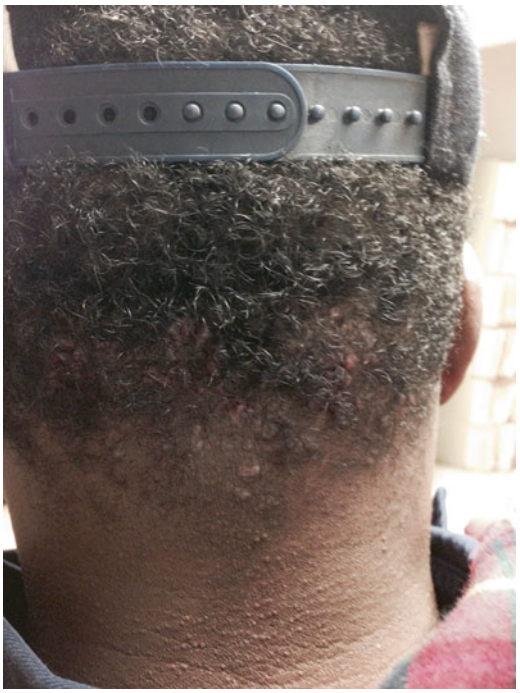

Fig. 16.1 Clinical appearance of acne keloidalis nuchae in a 17-year-old male with disease for 2 years. Note the presence of lichenified plaques, papules, and keloidal lesions developing over the nuchal region extending upward into the scalp (photos courtesy of Barry L. Smith, MD and Dhaval Bhanusali, MD)

males can be affected and lesions can be seen rarely in Caucasian or female adolescents.

Lesions beginning before puberty or in persons older than 50 is uncommon [3]. Glenn et al. reported a prevalence of 0.45 % in the African-American population [4]. Knable et al. found a prevalence of 8.2 % (13.6 % blacks, 0 % in whites) in an all male American football player population in Indiana aged 14–27 years old, with players beyond the high school level 10.3 times more likely to have AKN than at the high school level. Additionally, they found that black players were 8.5 times more likely to have AKN lesions than white players. Football players appear to be at higher risk due to friction and irritation from their helmets [5].

The incidence of AKN has been reported to be 9.4 % in Nigeria [2], 3.5 % in Cape town (10.5 % in men and 0.3 % women) [6], and 0.7 % in Benin [3]. In an Afro-Caribbean population in Jamaica, AKN was the eighth most common dermatosis, accounting for 1.74 % of all skin diseases in a dermatological clinic [7]. In a dermatology clinic in London, AKN was the most frequently seen disease among adult black patients, consisting of 13.7 % of their referrals [8]. South African school children had a prevalence of 0.67 %, exclusively in boys [9]. Additionally, while males are particularly affected, cases have been reported in females, with a sex ratio estimated at 20:1 [10].

Clinical Presentation

- **Acne Keloidalis Nuchae is a disorder of the ventral head and neck**
- **Pustules and papules at the follicular orifices typify early lesions**
- **Late-stage lesions can progress to abscesses, keloidal nodules, and scarring alopecia**

AKN is a disease of the hair follicles of the ventral head and neck. Diagnosis is based on typical clinical appearance and location. AKN is characterized by follicular-based papules and pustules over the occipital/nuchal areas of the scalp, as well as on the nape of the neck. Early AKN lesions will present as dome-shaped papules 2–4 mm in the nape or occipital scalp. They are usually asymptomatic, but pustules may also occur which often may be pruritic or painful. Broken hair shafts or ingrown hairs can be seen within or at the margin of the plaques. They will not be present for long periods due to patient's tendency to scratch early lesions off.

Lesions of AKN often heal with keloids, hence the origin of the name. Small keloidal lesions can cause scarring alopecia and may coalesce into larger plaques that are a few centimeters large [11]. Tenderness to the touch may be associated with inflammatory lesions of AKN. Scarring alopecia can result in complete loss of hair or scarred follicles with altered growth tracts and multiple hairs erupting from the keloidal lesions.

Keloids formed in the setting of AKN are likely to spread beyond the site of initial appearance and may ultimately coalesce and develop into tumor-like masses. Advanced cases may progress to form abscesses and sinus tracts. Purulent discharge may occur. Subcutaneous abscesses with draining sinuses may be malodorous.

Comorbidities (Table 16.1)

Salami et al. found that 60 % of patients thought about their lesions all the time, while 40 % have poor sexual relations [2]. Additionally, the pustular lesions may be pruritic and painful.

Table 16.1 Comorbidities of AKN

Acneiform lesions
Alopecia (scarring)
Infection
Intrusive thoughts
Pain
Poor sexual relations
Pruritus
Malodor
Self-consciousness
Tenderness

Differential Diagnosis

The differential diagnosis includes acne conglobata, acne vulgaris, acneiform eruptions, bacterial folliculitis, folliculitis decalvans, hidradenitis suppurativa, dissecting cellulitis and perifolliculitis capitis abscedens et suffodiens. Although these illnesses bear some similarity to AKN, the clinical features of AKN are extremely characteristic in most cases; in particular the location and the morphology of lesions are often distinctive.

Etiopathogenesis

The exact etiology of AKN is unknown, although several hypotheses have been suggested and the pathogenesis appears to be multifactorial. Shapero et al. postulate that folliculitis is mechanically induced by rubbing, scratching, or irritation and chronic folliculitis results in healing with scar and keloid formation [12]. This is supported in an analysis of 453 football players in Indiana; 13.6 % were positive for AKN, suggesting friction from helmet padding [5].

Hair cuts seem to be an inciting factor in many cases. 90 % of AKN consultations at a clinic in Nigeria had preceding haircuts [2]. In a study of 1,916 patients in Cape Town, South Africa, the highest prevalence was among those who receive haircuts using razors or clippers, and especially among those who experienced bleeding trauma from closely shaven haircuts [13]. Finally, in another South African study of 1,042 school children, prevalence was higher in those who received frequent haircuts, confirming this as a risk factor [9].

Kelly suggests that AKN may share similarities with pseudofolliculitis barbae, a follicular disorder of the beard area, common among African-American men who shave with razors. When tightly curled hair, common to Blacks/African Americans, is shaven, newly curled hair may have growth under the skin (ingrown hairs), causing a chronic progressive foreign body inflammatory reaction [10]. However, in a blinded study of histological AKN slides, no evidence was found of ingrowing hairs curving into the skin. Instead, Sperling et al. suggest that AKN is a primary scarring alopecia [11]. Additionally, no histological evidence was found by Sperling et al. of a transepithelial canal as suggested by Goette and Berger [14].

George et al. suggest AKN is frequently associated with male gender, seborrheic constitution, early reproductive years, and increased fasting blood testosterone [15]. AKN is also associated with lichen simplex chronicus with fibrotic keloidal scarring [16]. It has also been associated with acne mechanica by Knable et al. [5]. However, the hallmark of acne mechanica are comedones, which are absent in AKN [15]. AKN and acne keloidalis-like lesions is also associated with low-grade bacterial infection, superinfection [15], autoimmune processes, anticonvulsant medications [17], and physical or emotional stress [18].

AKN has also been described in two patients with keratosis follicularis spinulosa decalvans [19, 20], and as a cutaneous marker for metabolic syndrome [21]. Cases have also occurred in Caucasian patients after cyclosporine use, suggesting that the follicle is the primary site of initial lesions [22, 23].

Histologically, there is follicular and perifollicular inflammatory infiltrate, which changes composition with the progression of AKN. Initially, the infiltrate is composed primarily of neutrophils and lymphocytes in the lower infundibulum and isthmus of the hair follicle, and some reports mention the predominance of mast cells early on. As the lesion advances, the hair follicle and sebaceous glands rupture and granulomatous infiltrate develops around the free hair fragment. Dermal fibrosis and scars are seen here as the hair continues to proliferate beneath fibrous tissue [24]. Scarring alopecia may occur, which may be seen by dermal fibrosis associated with numerous plasma cells. Also as AKN is not a true keloid, keloidal collagen will not typically be found.

There is currently no evidence of a genetic component to AKN. However, there are twice the number of mast cells in the posterior scalp relative to individuals with AKN [15]. This higher density may contribute to pruritus and thus mechanical manipulation of the region, thus suggesting a genetic predisposition. Furthermore mast cells are often present in keloids and may aggravate disease.

Treatment

- **Treatment begins with lifestyle alterations that reduce nuchal trauma (including shaving and looser collars)**
- **Usage of topical antibacterials and other acne medicaments can help clear pustular lesions**
- **Cosmetic therapies can be used to clear keloidal lesions such as intralesional corticosteroids and laser hair removal**

Numerous methods have been used to treat AKN with success, and there currently is no gold standard for first-line therapies. First and foremost, prevention and education are the keys to management. Patients should be aware that closely shaven haircuts, collared shirts, athletic headgear, and general mechanical irritation of the area exacerbate the condition. However, once lesions appear, therapy must be initiated as soon as possible to improve long-term cosmetic outcomes [10].

Hair greases and hair pomades should be discontinued, and daily shampooing with benzoyl peroxide washes, chlorhexidine, or mild keratolytic cleaners containing alpha hydroxyl acids or tar are effective and should replace standard shampoo products [25].

Early to mild papular lesions may respond to topical corticosteroids. A class I or II corticosteroid (e.g., clobetasol propionate 0.05 %) gel, solution, or foam should be applied twice a day. A recent open-label study found clobetasol propionate 0.05 % foam to be effective for mild to moderate lesions [26]. Corticosteroid gels may also be combined with topical retinoic acid gel every night to relieve symptoms and flatten lesions.

Topical clindamycin or erythromycin solution or gel can be used twice daily for inflammatory lesions, including papules and pustules, until inflammation subsides. Imiquimod 5 % has been described as beneficial for prevention of keloid recurrence after excision; however, the usage of topical Imiquimod 5 % for keloidal lesions of AKN has not been reported extensively in the literature [27, 28].

For mild to moderate cases, intralesional corticosteroids, usually diluted triamcinolone acetonide (e.g., kenalog 5–10 mg/cc), are injected at 3- to 4-week intervals. Long-pulsed Nd-YAG laser assisted hair removal via coagulation necrosis of hair follicles [29–31] and laser hair epilation with the diode laser [32]. For keloidal lesions or resistant papules, cryotherapy or carbon dioxide laser has been shown effective for refractory AKN. Most laser treatments shrink or destroy the hair follicle and therefore eliminate the nidus of inflammation [18].

For severe plaque and tumor stage AKN, surgical management may be best. Approaches include excision with grafting, excision with primary closure [33], excision with secondary healing [4, 34], and staged excision with primary closure. Surgery has proved to be an effective approach, but it must be noted that the tissue must be removed such that the base of the hair follicle is not presenting in order to prevent recurrence. The large open area resulting over the occipital/nuchal scalp is then left to heal via secondary intention [35].

Clinical Studies/Workup

No specific tests other than histology are available for AKN (histopathology in pathogenesis section). If any pustules or draining sinuses, bacterial cultures should be taken and appropriate antibiotics prescribed.

Ongoing Research

No major clinical trials are under way for acne keloidalis nuchae.

Conclusions

Acne Keloidalis Nuchae is a chronic perifollicular inflammatory process marked by papules and pustules in the nuchal region. It can present as keloid-like plaques with tufted hairs in the margins, and over time can grow to become disfiguring and painful. Early disease intervention may prevent the formation of tumor-like masses that can abscess and become malodorous. These lesions are known to have significant aesthetic and cosmetic impacts [2]. Though it most frequently presents in young men of African descent, it can also be seen in men and women of all racial backgrounds. The exact etiology is unclear, but the condition may be due to constant friction from athletic headgear [5] and close shave haircuts [13]. Treatment should begin promptly and include topical corticosteroids with or without topical retinoids for mild lesions, topical and oral antibiotics for pustular lesions prescribed after a culture is obtained, and intralesional dilute triamcinolone acetonide in moderate cases. For advanced cases, surgical excision has been shown to be effective.

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Pseudofolliculitis Barbae

17

Nanette B. Silverberg

Abstract

Pseudofolliculitis barbae is a chronic inflammatory folliculitis of the beard area that occurs after onset of puberty. Lesions are most common in males, but can occur in females with terminal hair growth on the chin area, the latter warranting hormonal evaluation for signs of androgen excess. Onset of pseudofolliculitis barbae begins after initiation of hair removal in the chin and beard area by shaving and/or plucking. Lesions are a result of ingrowth of the hairs causing inflammatory lesions such as papules and pustules and eventually fibrosis, scarring alopecia, and sometimes keloidal type scars. Therapy can include avoidance of shaving, usage of specialized shaving equipment that prevents an aggressively close shave, and application of acne therapies as well as anti-inflammatory agents. In medically resistant cases, long-pulsed hair removal lasers, e.g., Nd:Yag, have been described as adjunctive therapies for clearance of lesions.

Keywords

Pseudofolliculitis barbae • Razor bumps • Keloids

Introduction

Pseudofolliculitis barbae (PFB) is a chronic inflammation of the glabrous skin of the chin and neck, which appears in areas of shaving and/or plucking. Lesions are noted primarily in males of color. The cause of the condition is not fully understood, but is believed to relate to ingrowth and incurling of the curved hairs into the follicle wall, causing inflammation and potentially scarring [1, 2].

Epidemiology

- **PFB is a condition of the hair follicle affecting postpubertal males**
- **Affected males are usually Black or Hispanic**
- **Some females are affected, suggesting the need for endocrinologic work-up**

Pseudofolliculitis barbae (PFB) is noted after puberty with the onset of the mature beard formation over the chin and neck in males with curled hair (Fig. 17.1), as well as females with the same, the latter relating to familial hirsutism or rather due to endocrinologic abnormalities, e.g., PCOS. PFB affects 45–83 % of African-American males [3].

Clinical and Pathogenesis

- **Papules and pustules occur over the chin and neck in early lesions**
- **Scarring alopecia, hypertrophic scars, and keloidal scars can occur in late lesions**

Hairs involved over the chin and neck are usually curled. Shaving or plucking cuts hairs on an angle. The hairs then curl inward retracting into the follicle where they incite a foreign body reaction. This results in acne formation (e.g.,

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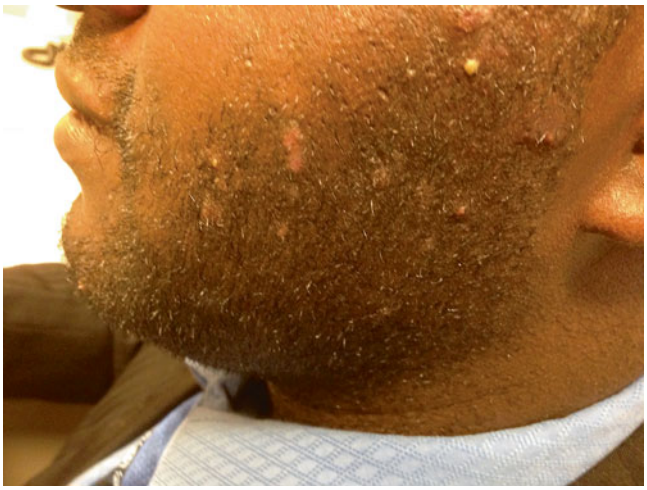

Fig 17.1 Beard area of a young Hispanic adult male demonstrating follicles papules and pustules, as a result of shaving

papules and pustules), with fibrosis of the follicle, scarring alopecia, and eventually keloidal scar formation in some susceptible males [4]. Magnification will reveal a trapped hair in the follicle in early lesions prior to inflammatory response to the trapped hair.

Some therapies and illnesses are known to affect the appearance of PFB. Medications promoting hirsutism including cyclosporine [5] and oral minoxidil [6] can initiate PFB formation. Renal transplant patients may note hyperplastic PFB lesions [7]. Scar sarcoidosis can occur in PFB lesions [5]. Pathogenesis may relate in part to mutation in hair follicle-specific keratin, the K6hf polymorphism [8, 9].

Therapy

- **Prevention can be performed with proper shaving techniques and equipment**
- **Topical acne therapies can be used to treat active lesions**
- **Resistant lesions can be treated with hair removal laser or avoidance of shaving**

Topical therapy includes steaming the cheek before shaving, freeing trapped hairs with a tweezer, and application of benzoyl peroxide-based shaving cream to the face prior to shaving. Shaving should be performed using a specialized razor with a grid over the blades to reduce aggressively close shave, stroking the beard with the blade in the direction of the grain of the hair and following shaving with acne therapies, e.g., topical clindamycin/topical benzoyl peroxide combination agent [10], topical retinoids, and/or topical antibiotic agents [11, 12]. Emollients and exfoliants to open the follicle can aid in avoidance of skin lesions. When conservative measures fail, hair removal laser with long-pulsed diode, alexandrite, or long-pulsed Nd:Yag lasers can be used to reduce hair thickness and growth in the inflamed follicles as well as to reduce dyspigmentation, papule formation, and cobblestoned appearance. Long-pulsed lasers are used to reduce risk of absorption by cutaneous melanin and consequent depigmentation. Dosages should be conservative to avoid induction of dyspigmentation in the darkest patients [13–16]. Photodynamic therapy has also been described for lesion reduction [17]. Eflornithine can be used to reduce hair size and enhance results from laser [18]. Hydroquinones and other lightening agents with adjunctive sun protection can be used for post-inflammatory pigmentary alteration. Intralesional corticosteroids in dilute concentrations can be used to reduce the size of hypertrophic scars and keloidal lesions [19, 20]. In the event of lack of response, shaving can be stopped altogether and can be replaced by depilatories [21, 22]. Isotretinoin has been described as being mildly successful at lesional clearance temporarily as well [23].

Although few older men are noted to have PFB, disease can be active from adolescence through senescence. In women, a thorough medical history for hair-inducing drugs or hormonal abnormalities (e.g., irregular menses, deep voice) is needed and diagnosis may merit laboratory evaluation and/or endocrinological referral.

Conclusions

PFB is a chronic inflammatory disease of the hair follicles of the face and chin resulting from shaving. A plethora of therapeutic options exist, but prevention in the form of careful hair care is best for disease control.

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Part IV

Infections in Children of Color

Tinea Capitis in Children of Colour

18

Catherine C. McCuaig

Abstract

Tinea capitis is a common infection of the scalp and scalp hairs that produces a variety of symptoms including hyperkeratosis and alopecia. Causative agents cary worldwide but *Trichophyton tonsurans* has emerged as a significant cause. Therapies include fomite reduction and oral antifungals.

Keywords

Tinea capitis • Scalp ringworm • Paediatric dermatophytosis • *Trichophyton* (*T.*) • *Microsporum* (*M.*) • Terbinafine • Griseofulvin • Itraconazole • Fluconazole • Asymptomatic carriers

Background/Introduction

Tinea capitis is due to an infection of the hairs of the scalp caused by superficial fungi (dermatophytes) of the genera *Microsporum* or *Trichophyton*. Synonyms include scalp ringworm and 'Tinea tonsurans' [1]. Tinea capitis is characterised by hair loss, with accompanying scaling, hyperkeratosis, and at times inflammatory patches, pustules, and plaques. World incidence has reached epidemic rates and now varies from 4 to 15 % [1].

Epidemiology/Demographics

- **Tinea capitis is the most common paediatric worldwide superficial mycosis with epidemics ranging from 4 to 15 % of the population and pathogenic organisms depend on geographical region.**
- **Anthropophilic tinea infections spread between humans of whom asymptomatic carriers and fomites may harbour fungus, and these are increasing with urbanisation and immigration.**
- **Zoophilic dermatophyte infections are more common in rural settings, where pets, rodents, and livestock may infect humans.**

Tinea capitis is the most common paediatric dermatophyte infection throughout the world [2] World incidence has reached epidemic rates and now varies from 4 to 15 %; frequency of *Trichophyton (T.) schoenleinii* has been decreasing [1, 3, 4]. There is a slight male predominance [1]. Tinea capitis affects primarily prepubertal children with a peak incidence of 3–10 years, and less commonly adults [1]. Postpubertal children and adults are at least partially protected by the increased sebum with fatty acids which are fungistatic [1, 2]. The fluctuations in the causative agent of tinea capitis may be due to the environment, human migratory patterns and immigration, new therapies, and pathogen and host factors [2, 5–7].

The dermatophytes involved may be acquired by human contact (anthropophilic) or contact with an infected animal (zoophilic). There has been a significant worldwide rise in the incidence of infections caused by anthropophilic dermatophytes and a relative decrease of the zoophilic ones in childhood tinea

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Table 18.1 Geographic location and ethnicity defines the predominant organism responsible for tinea capitis

Country	Dermatophyte predominant
The Americas (especially African Americans)	*T. tonsurans*
Australia, New Zealand	*T. tonsurans*
The United Kingdom	*T. tonsurans*
Europe	*M. canis*
West Africa	*T. soudanense*
East and North Africa	*T. verrucosum*
Asia (China), Middle East, India	*T. verrucosum*, *M. canis*, *T. schoenleinii*

capitis, as the population becomes more urbanised [7]. The anthropophilic organisms include *Microsporum (M.) audouinii*, *T. tonsurans*, *T. soudanense*, *T. violaceum*, and the anthropophilic variant of *T. mentagrophytes* [2, 7].

Whereas cats and dogs harbour *M. canis*, *T. verrucosum* is found in cattle, and zoophilic strains of *T. mentagrophytes* (now called *T. interdigitale*) are transmitted by a variety of rodents including mice, guinea pigs, hedgehogs, rabbits, and chinchilla. Of note, these *T. mentagrophytes* infections have been dubbed 'cuddly toy mycosis' [8]. The subspecies include *var. granulosum* (rodents), *var. erinacei* (hedgehog), and *var. quinckeanum* (mice) as well as *Trichophyton* species of *Arthroderma (A.) benhamiae* found in small rodents, most commonly in guinea pigs [9–11]. Zoophilic *T. mentagrophytes* have been a cause of neonatal kerion in two Caucasian infants in Argentina [12].

Epidemiologic studies of tinea capitis have been performed worldwide and indicate changing trends and an evolution in the types of species most frequently involved [2] (see Table 18.1). In the United States, Canada, Mexico, Jamaica, Central America, Ireland, and Brazil, *T. tonsurans* has replaced *M. audouinii* and *M. canis* as the most common cause of tinea capitis since the 1960s [2, 13–17]. In the United States, a study of children in Northern California 1998–2007 demonstrated that the annual incidence decreased according to prescriptions, and that the majority of affected patients were African-American with the overwhelming dermatophyte *T. tonsurans* (91.8 %), followed by *M. canis* at 3 % [1].

In contrast, *M. canis* is the most frequent pathogen in Europe [3, 18–20]. *M. canis* has remained most prevalent around the Mediterranean and specifically bordering countries like Belgium [3], Austria, Hungary, Germany, Poland, and Israel [6] as well as Saudi Arabia and Puerto Rico [2]. Anthropophilic tinea capitis is increasing mainly in urban areas in Europe, with *T. tonsurans* prevalent in the UK [21, 22] and Ireland [15] and increasing in Poland [23] and in Spain [24] second only to *M. canis*, and *T. soudanense* and *M. audouinii* in France [6]. In the UK from 1980 to 2005, frequencies of isolations of zoophilic fungi from scalp infections decreased by 90 % (*M. canis*, *T. verrucosum*, *T. mentagrophytes var. mentagrophytes*) while anthropophilic *T. tonsurans* and *T. violaceum* increased by 1,000 % over the same period [21]. *T. violaceum* is taking hold probably due to immigration from Africa and India, with reports common in Romania [25], Italy [26], Sweden [27], Portugal, Spain [28], Russia, Greece [3, 29], and Yugoslavia [6, 28]. In Sarajevo and Bosnia, over 10 years up until 2006, tinea capitis was due to zoophilic dermatophytes (91.8 %); primarily *M. canis* prevailed over anthropophilic (7.2 %) *T. schoenleinii* (2.4 %) and *T. violaceum* and geophilic (1.0 %) dermatophytes [30]. In Kuwait, *M. canis* also predominates with 62.5 % followed by *T. violaceum* with 19.3 % and *T. tonsurans* with 13.1 %, with *T. rubrum* being the least frequent [31].

T. violaceum and *M. canis* are prevalent agents in Asia, India, and the Middle East [2, 5, 7, 28]. In a 16-year (1993–2008) review in southeast China, *M. canis* (62.4 %) was predominant, followed by *T. violaceum* (19.0 %), and *T. tonsurans* (9.8 %) with notable absence of *T. schoenleinii* [32]. However, in a rural area of western China, five species were identified in school-aged children (in order of frequency: *T. violaceum*, *T. schoenleinii*, *M. ferrugineum*, zoophilic strains of *Arthroderma vanbreuseghemii*, and *T. tonsurans*) [33]. *T. violaceum* has been reported to be the most frequent cause of tinea capitis in India [34].

T. schoenleinii which causes favus was once quite common; however the worldwide incidence has decreased except in some regions of China, Nigeria, and Iran [4]. In Iran up until 2001, *T. violaceum* was the most common aetiological agent (37.3 %) followed by *T. schoenleinii* (21.5 %), *M. canis* (18.6 %), *T. verrucosum* (14.8 %), *T. tonsurans* (5.3 %), *T. rubrum* (1 %), *M. gypseum* (1 %), and *T. mentagrophytes* (0.5 %). Increased incidence was correlated with poor socioeconomic position and large family size [7].

In Africa, predominant dermatophytes causing Tinea capitis in children are: *T. violaceum* from north and east Africa including Ethiopia and Egypt [35], *T. soudanense* from West Africa, and *M. canis* are commonly isolated [2, 36]. *T. verrucosum* is found especially in males from rural areas in Morocco [37]. In a study from the Ivory Coast conducted in school-aged children during a 10-month period, 2007–2008, 2,458 of 17,745 (overall prevalence of 13.9 %) had positive cultures with the most prevalent aetiologic agents *T. soudanense*, *M. langeronii*, and *T. mentagrophytes* (56.7 %, 21.4 %, and 19.7 %, respectively) and occasional *T. violaceum* (1.4 %) and *T. rubrum* (0.8 %) [38].

Although *T. tonsurans* remains the primary dermatophyte causing tinea capitis in the United States, reports of *T. violaceum* and *T. soudanense* have been sporadic. Twenty-four cases of *T. violaceum* and *T. soudanense* were reported in Baltimore, MD, USA, between 2003 and 2006, traced primarily to immigrants from West Africa [39]. A retrospective review

of 189 cases in 2001–2006 in Columbus, OH, showed that tinea capitis was primarily in African Americans and *T. tonsurans* (88.9 %) was the main causative agent followed by *T. violaceum* (4.2 %) [36]. In a 1949 series from Boston, MA, *T. violaceum* was reported to have caused a single case of tinea capitis among 78 cases of fungal scalp infection [28]. Among subsequent reports in the 1950s and 1960s were three outbreaks of tinea capitis due to *T. violaceum* occurring in a state school in New York [40] and among family members in Detroit, MI [3] and in Texas [29]. Another report from Detroit investigators in the late 1960s described two adult patients with tinea corporis caused by *T. violaceum* [41]. In Australia, *T. tonsurans* caught up with *M. canis* by 1993, and later reports of *T. violaceum* in Ethiopian, Mediterranean immigrants, and aboriginals have surfaced [42, 43].

Published reports of *T. soudanense* infections in the United States have been even more infrequent. Two sisters adopted from Liberia were reported in 2003 in Cincinnati, OH, USA, with tinea capitis due to *T. soudanense* [44]. Although more recent reports describing infections in the United States due to either *T. violaceum* or *T. soudanense* are rare, similar trends have been observed in other countries. In New Zealand, where *M. canis* is the common cause of tinea capitis, 60 cases were reported of primarily *T. violaceum* and occasional *T. soudanense*, most of whom were East African refugees from Somalia [40]. Studies from Sweden, Finland, and Belgium have also reported isolation of *T. violaceum* and *T. soudanense* from children with tinea capitis, most of whom were African (particularly Somali) immigrants [27, 41, 45].

T. rubrum, which is the most common dermatophyte isolated worldwide, is an uncommon cause of tinea capitis, but has been reported in several newborns [12, 46–48]. These were reported in Caucasians only, one Greek, one Italian, one Argentinian, and one Asian infant.

Anthropophilic Dermatophyte Infections

Anthropophilic fungi are generally transmitted from person to person with spread occurring more frequently in conditions of overcrowding, cosleeping, poverty, and poor hygiene [7, 49]. Certain sports have been linked with spread of tinea capitis through judo in Japan [50] and France [51], and wrestling in Turkey [52]. In addition, fomites such as combs, brushes, and hair-trimming tools may bear the infected spores [53].

Schools, nurseries, and daycares have reported endemics of tinea capitis; in an outbreak in a Swiss school where three cases of tinea capitis were identified to be due to *M. audouinii*, three family members and five other classmates were found to be asymptomatic carriers of *M. audouinii* and were treated to prevent further spread [54]. All 27 children with tinea capitis in a primary school in Madagascar due to *M. langeronii* had contact with an infected schoolmate and 70 % reported to have infected brothers and sisters at home [55]. Tinea capitis is endemic among schoolchildren from Gabon where they have reported 20–26 % incidence, primarily due to anthropophilic species: *T. soudanense* (29.4 %) was the most prominent species, followed by *T. tonsurans* (27.9 %) and *M. audouinii* (25.0 %) [56]. In a *T. tonsurans* outbreak in a nursery in England, 12 children developed tinea capitis and 7 staff members tinea faciale or corporis [55].

Asymptomatic Carriers

Asymptomatic individuals with high spore load of *M. audouinii* [54], *T. violaceum*, or *T. tonsurans* may be important vectors in the transmission of scalp ringworm because they have the potential to shed large numbers of spores over long periods of time and may be risk factors at both home and school [57]. The prevalence of asymptomatic carriage differs between geographic regions with a rate of 0.1–49 % [57]. In London, England, more than 200 household contacts of children with *T. tonsurans* tinea capitis were screened; 7.2 % had clinically evident disease, yet 44.5 % had silent fungal carriage on the scalp, most commonly in children less than 16 years of age [22]. One study in the United States demonstrated an overall carrier incidence of 4 %, with the highest incidence of 12.7 % among girls of African-American descent [58]. Another from Milwaukee, WI, with *T. tonsurans* tinea capitis reported asymptomatic carriage by household contacts of a child with tinea capitis at 16 %, with 41 % of carriers persisting up to 2 months; 32 % of families had at least one member who was a carrier [49].

Clinical Presentation

- **Hair loss (alopecia)**
- **Scalp hyperkeratosis**
- **Inflammatory**

If both 1 and 2 are present, odds ratios 7.5 for tinea capitis

The clinical pattern of presentation of paediatric tinea capitis depends on the type of infection of the hair shaft as well as the immune response of the host (see Table 18.2). It is often asymptomatic but may be pruritic and even painful if a kerion is present. Involvement is usually patchy; however, it can involve the entire scalp. An endothrix infection by *Trichophyton* often leads to hair breakage causing a 'black dot' pattern with minimal apparent inflammation (see Figs. 18.1 and 18.2) [59]. In contrast, *M. audouinii* which has an ectothrix invasion will show 'grey patch' scaling and alopecia (Fig. 18.3a, b) [59]. Patients vary from a seborrhoeic

Table 18.2 Clinical presentation of tinea capitis

Non-inflammatory
Black dot
Diffuse seborrhoeic dermatitis-like (dandruff-like)
Grey patches with alopecia
Inflammatory
Pustules
Kerion
Favus

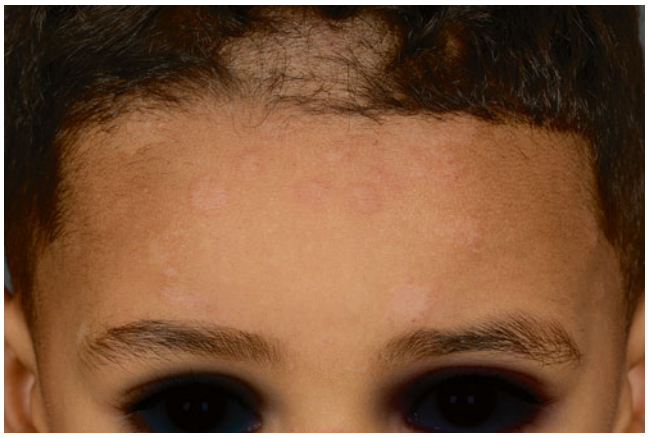

Fig. 18.1 Black dot tinea capitis with annular lesions of tinea faciei

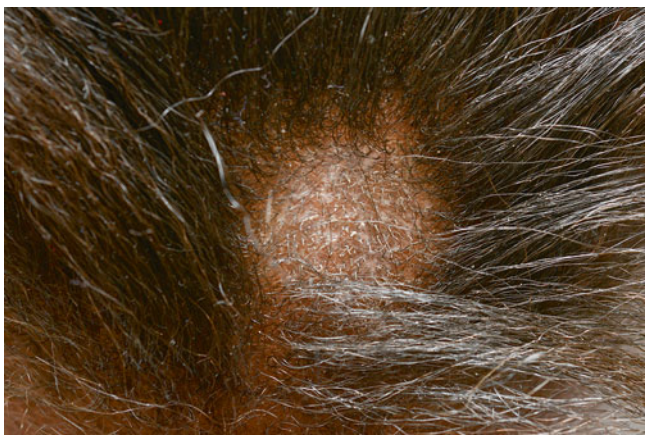

Fig. 18.2 Non-inflammatory tinea capitis with localised alopecia

dermatitis pattern to occasional pustules and a boggy plaque kerion (Fig. 18.4). Favus is described as a honeycomb pattern of yellowish thick cup-shaped 'scutula' that coalesce to form plaques on the scalp with underlying alopecia and is caused primarily by *T. schoenleinii* (90 %) [4]. *T. violaceum*, *T. verrucosum*, zoophilic *T. mentagrophytes* (referred to as '*var. quinckeanum*'), *M. canis*, and geophilic *M. gypseum* have also been recovered from favic lesions [4]. Both favus and kerion can lead to permanent alopecia. Posterior cervical, auricular, and occipital adenopathy may be present in tinea capitis but is not as essential a finding as once thought [14, 60]. In as many as one-third of cases, annular lesions of tinea faciale or corporis may be found at a distance, in the individual [15] as well as family members.

According to a 2011 review of 164 children in New York, USA, scalp hyperkeratosis is usually associated with tinea capitis in Black and Hispanic children [14]. This is in contrast to prepubertal Caucasian children, in whom the most common cause of scalp scaling was found to be seborrhoeic dermatitis (54.5 %) followed by atopic dermatitis (24.2 %) and was often accompanied by cervical adenopathy [61]. When scalp hyperkeratosis is accompanied by alopecia in children of colour, the odds ratio for tinea capitis is 7.5 [14]. In a study of 68 primarily African-American children of tinea capitis in an urban setting Norfolk, VA, USA, positive likelihood ratios were 7.5, 3.3, 1.4, and 1.1 for the presence of adenopathy, alopecia, pruritus, and scaling, respectively, for cultures positive for dermatophytes, all *T. tonsurans* [60].

Acne keloidalis has been described as a novel presentation for tinea capitis in adults [62, 63] and misdiagnoses of impetigo, folliculitis, recurrent furunculosis, pyoderma, folliculitis decalvans, tufted hair folliculitis and dissecting cellulitis has been in the differential diagnosis of some cases of inflammatory tinea capitis [64].

A dermatophytid is a disseminated eczematous eruption which may occur in 5 % of tinea infections before or after initiation of systemic antifungal drug therapy and is not an indication for stopping medication [65]. It is thought to be a delayed type hypersensitivity reaction to the dermatophyte antigen. The eruption may be limited to the face or may be quite widespread, and is composed of monomorphic papules, vesicles, pustules, or pityriasis-like oval patches (Figs. 18.5, 18.6, and 18.7) [65]. Topical and oral corticosteroids and antihistamines may be needed to treat dermatophytids and pruritus; however systemic antifungal therapy must also maintained [65].

Investigations

Complementary investigations can be performed after clinical examination for type of hair loss and/or scale, cervical and occipital adenopathy, and distant tinea faciei or tinea corporis. **Wood's light** can be performed to support the diagnosis of tinea capitis. It shows positive fluorescence of the infected hairs in the cases of ectothrix (i.e. *M. canis* or *M. audouinii*) (Fig. 18.8) or favus infections, and is absent in the *Trichophyton* endothrix hair shafts.

Dermoscopy is a method of increasing importance in the diagnoses of tinea capitis in coloured children in whom erythema is often absent [66, 67]. Corkscrew hairs as a specific dermoscopic sign of tinea capitis in blacks were first described by Hughes (Fig. 18.9a) [68]. In addition, the presence of

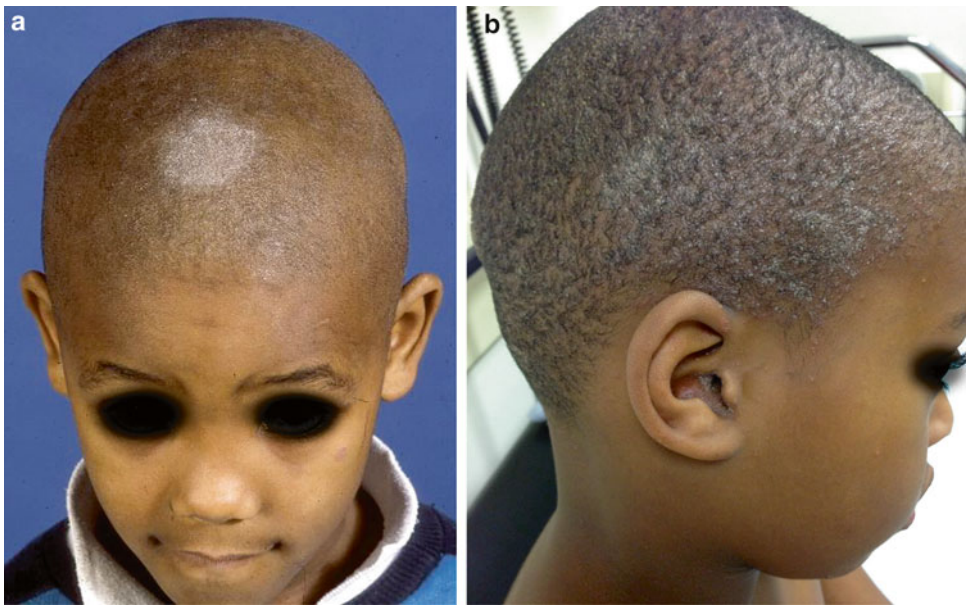

Fig. 18.3 (**a**, **b**) Scalp hyperkeratosis (*Grey*-patch form) of tinea capitis

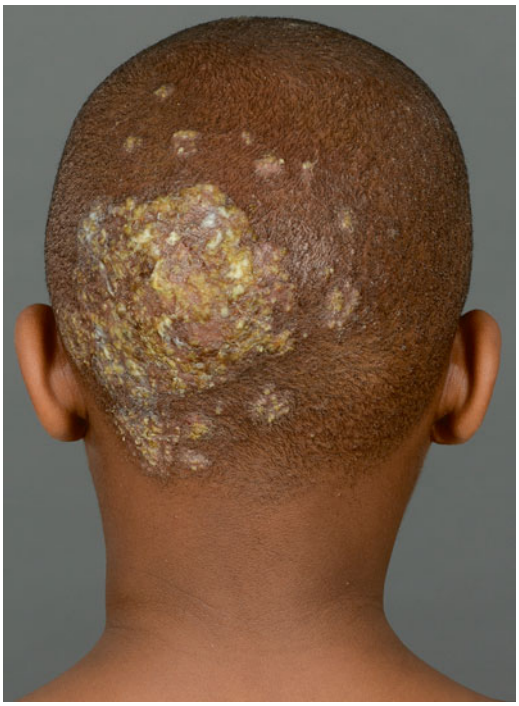

Fig. 18.4 Kerion and left post cervical adenopathy. Boggy pustular plaque dotted with pustules. Patient admitted for mechanical debridement, compresses, in addition to oral antifungal and antibiotic

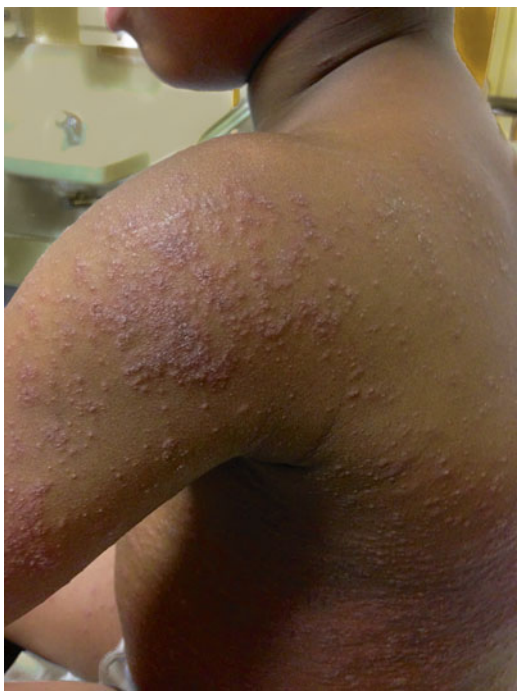

Fig. 18.5 Dermatophytid papulopustular lesions in patient no. 5

comma hairs in dark-skinned individuals helps clinch the diagnosis (Fig. 18.9b) [66, 67, 69].

Direct microscopic examination of scrapings of hair and scales mounted in 10–20 % potassium hydroxide solution may reveal fungal hyphae and spores; however it may not be performed due to time constraints (Fig. 18.10).

The gold standard to confirm diagnosis of tinea capitis is **culture** and establishes the subtype, which may have an impact on treatment choice and duration. The method to obtain the culture is varied. Scrapings, hairbrush, toothbrush, and cotton swabs may be used. A retrospective study of 391 children with suspected tinea capitis conducted during

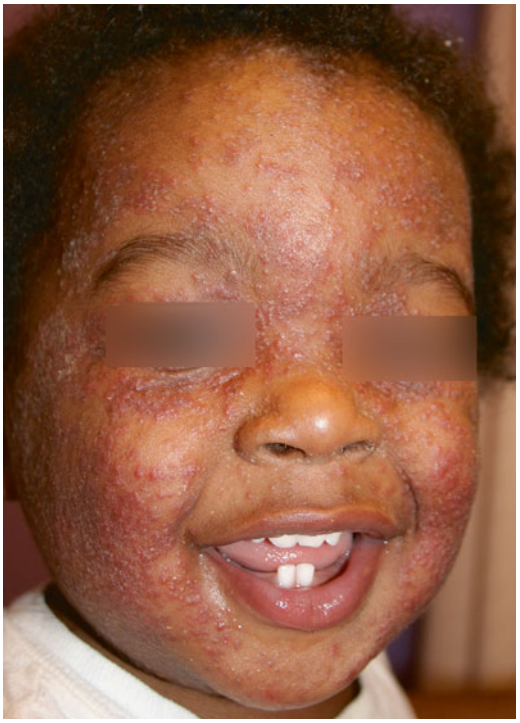

Fig. 18.6 Dermatophytid reaction on the face of a child (courtesy of Dr BA Cohen)

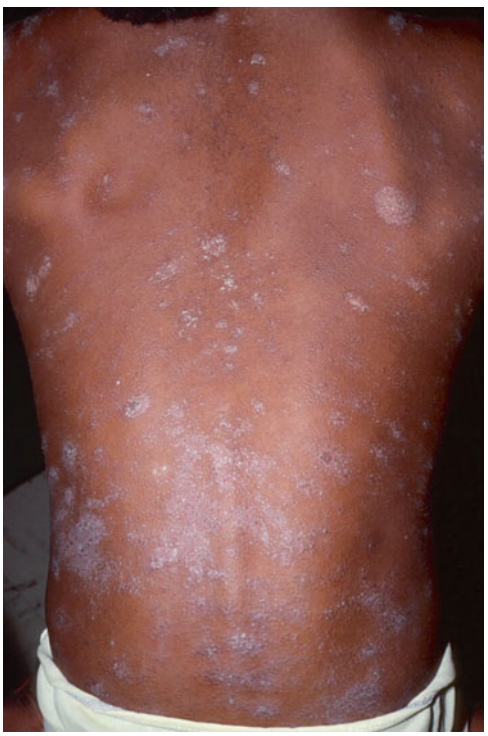

Fig. 18.7 Pityriasis rosea-like dermatophytid reaction on the trunk (courtesy of Dr BA Cohen)

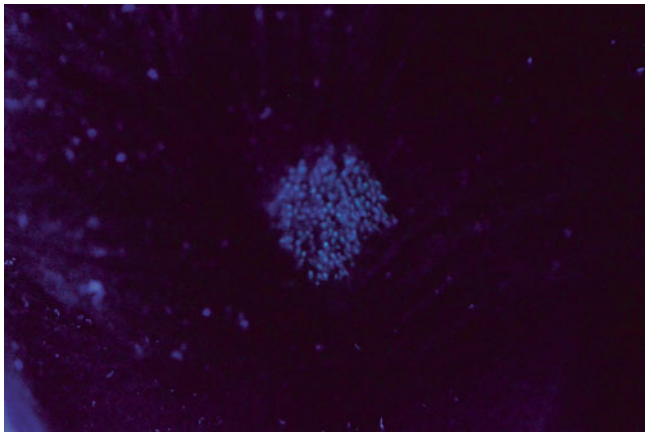

Fig. 18.8 Wood's light of tinea capitis shows florescence (*M. audouinii*)

6 years compared the hairbrush method with that of the scalp scraping method; the former was superior, with combination of the two methods increasing the yield of identifying the pathogen [70]. In another study, the hairbrush method had more yield than the toothbrush ($P<0.01$) and the cotton swab methods ($P<0.05$), and again using both methods provided a higher yield [71]. Although these studies indicate that the hairbrush technique is slightly better, in practice, the cotton swab technique is non-invasive and simple to perform in children, has a high yield, and has been adopted by many clinicians in their office [14, 72].

In a study of 135 children with tinea capitis, the cytobrush was superior to traditional scrapings for detection 97.7 % vs. 85.1 % and speed of growth 8.5 vs. 11.2 days [73]. The cytobrush is a sterile and commercial brush used routinely for cervico-vaginal smears known as the Papanicolaou technique ('Pap-smear') and it potentially costs US$0.006 + per unit, even less than sterile blades (US$0.012+), transport swabs (US$0.03+), and toothbrushes (US$0.05+) [74].

Treatment

- **Must always give oral antifungal therapy (4–8 weeks).**
- **Griseofulvin has advantages of lower cost, long safety record, and greater efficacy in *Microsporum* infections; however it may require longer therapy than terbinafine.**
- **Complementary therapy for the entire family is important for eradication of spores.**

Topical antifungal therapy is inadequate to eradicate tinea capitis because they do not penetrate the hair follicle [75]; however they are complementary to minimise further carriage

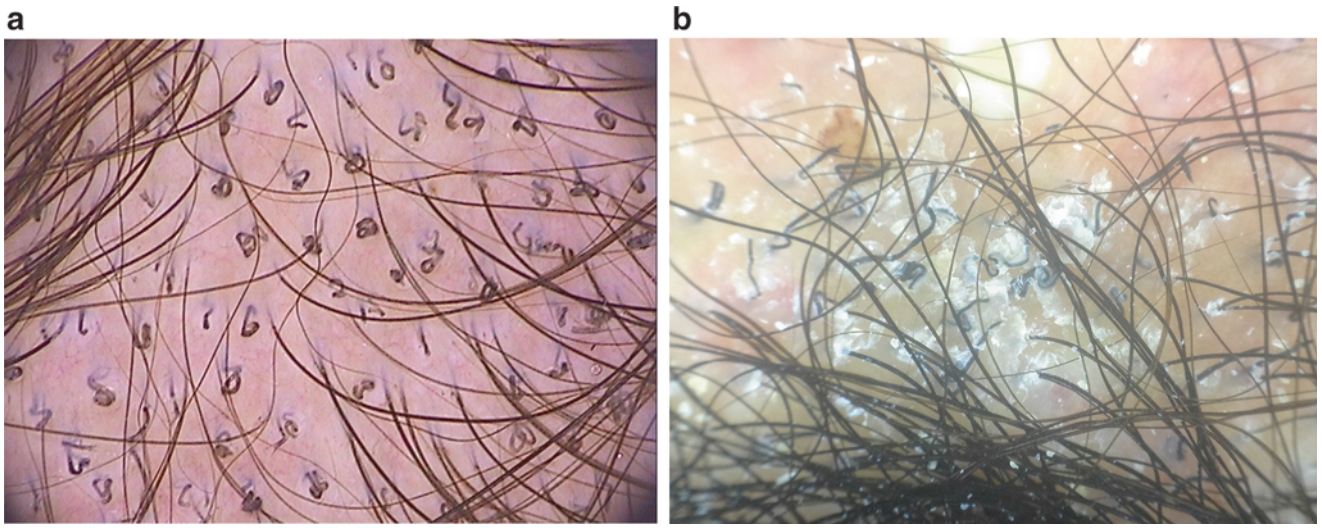

Fig. 18.9 (**a**) Dermoscopy (trichoscopy) corkscrew hairs (courtesy of Dr A Tosti). (**b**) Dermoscopy (trichoscopy) shows comma hairs and corkscrew hairs (courtesy of Dr.AM Pinheiro) 2× magnification

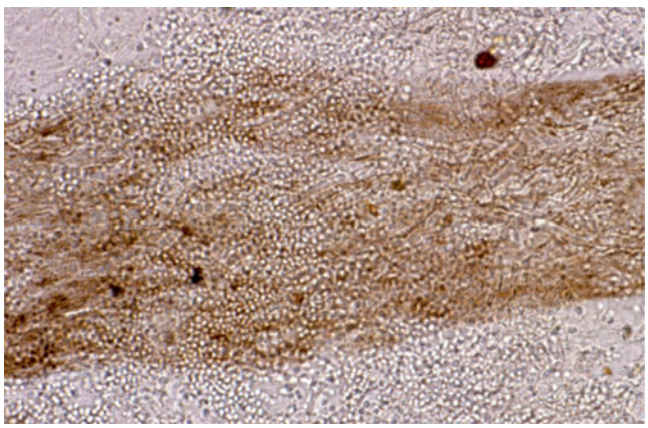

Fig. 18.10 Direct microscopy of ectothrix infection (courtesy of Dr. R Grimalt)

of spores (see Table 18.3). It has been reported for successful use in a neonate with *T. tonsurans* tinea capitis [76].

Systemic antifungals are absorbed through the hair papilla into the hair shaft [77]. Fungal spores located distally are inaccessible to the antimycotic agent [77].

Griseofulvin has been introduced in 1958, ever since it remained the gold standard for the treatment of tinea capitis in the United States [77]. It is fungistatic, preventing mitosis of fungal cells, and is best absorbed when taken with fatty food. Many studies use 10 mg/kg/day, which is inadequate for therapy of tinea capitis [77]. Higher doses of 20–25 mg/kg/day divided twice daily with food are recommended for the microsized griseofulvin vs. 10–15 mg/kg/day ultramicrosized, and there is some evidence that the crushable tablets may be more effective than the commercial liquid preparation [13, 78]. Most studies have a duration of 8 weeks [75, 78]. Its advantages include that it is inexpensive, has a long and good safety profile, and is more effective in treating Microsporum infections [78]. Griseofulvin is generally well tolerated in children, with rare nausea, headache, and rash [78]. If given longer than 8 weeks, hepatic and renal blood tests and complete blood count are recommended monthly. Unfortunately, a number of countries no longer have it readily available: Canada, Austria [77], Belgium, Greece, Portugal, and Turkey [75].

Terbinafine is an allylamine which is fungicidal by blocking ergosterol biosynthesis. Its advantages include shorter treatment times (2–4 instead of 8 weeks for griseofulvin), tolerability, and once-daily dosing irrespective of food [78]. The dosage is adjusted to: <10–20 kg 62.5 mg, 21–40 kg 125 mg, and >40 kg 250 mg daily for 4 weeks for tinea capitis due to *Trichophyton* spp. [77]. Terbinafine cannot be excreted by sweat contrary to griseofulvin and azoles, although it is present in sebum (postpubertal) and is incorporated into the anagen hair which may account for its reduced efficacy in ectothrix infections [77]. Higher dosages (10–25 kg: 125 mg/day; >25 kg: 250 mg/day or 12.5 mg/kg/day) or longer duration of treatment (8–12 weeks) may be required for *M. canis* infection [79]. It is safe; however plasma levels are reduced by rifampicin and increased by cimetidine [79]. A 2007 Cochrane review of systemic antifungal treatment for tinea capitis in children concluded that newer treatments, including terbinafine, have equivalent efficacy and safety profiles to griseofulvin and allow treatment to be shorter [78]. A subsequent randomised controlled trial found that complete

Table 18.3 Treatment of tinea capitis

ORAL ANTIFUNGAL
GRISEOFULVIN some evidence that capsules are more effective than liquid preparation [13]
Microsized: 20–25 mg/kg/day in bid dosing to a max of 1 g total × 8 weeks
Ultramicrosized: 10–15 mg/kg/day in bid dosing to a max of 1 g total × 8 weeks
TERBINAFINE
Regular (3–6 mg/kg/day):
Trichophyton: 20 kg, 62.5 mg; 21–40 kg, 125 mg; >40 kg, 250 mg daily for 4 weeks
M. canis: 10–25 kg, 125 mg/day; >25 kg, 250 mg/day or 12.5 mg/kg/day and 8 weeks or longer
Granulate: 5–8 mg/kg over age 4 years:
<25 kg, 125 mg/daily; 25–35 kg, 187.5 mg/daily; >35 kg, 250 mg/daily for 6 weeks
ITRACONAZOLE 3–5 mg/kg/day oral solution; 5 mg/kg/day capsules for 6 weeks
FLUCONAZOLE 6–8 mg/kg/day for 6 weeks
TOPICAL THERAPY *(complementary but not adequate alone)*
Shampoo: selenium sulphide 1 % [85], ketoconazole 2 %, ciclopirox 1–1.5 % zinc pyrithione 1–2 %, 2–3× per week for 1 year in the entire family
Povidone iodine 4 % solution
(**Antifungal cream**; imidazole, allylamine promoted by European countries in the first week) [75, 79]
Verification of siblings and classmates
Cleansing of fomites with bleach preparation and/or hot water

cure rates for *T. tonsurans* infection were significantly higher for terbinafine than for griseofulvin; however, griseofulvin remains the only licensed treatment for children in the UK. Nonetheless, many dermatology units in the UK use terbinafine as first-line treatment because it is highly effective and well tolerated, and adherence to treatment is high. A prospective, non-blinded, study of three commonly used drugs (terbinafine, griseofulvin, and fluconazole) was undertaken in 75 children aged <12 years with tinea capitis primarily due to *T. violaceum*, in New Delhi, India [80]. Of these, 60 % had non-inflammatory TC and 56 % had an ectothrix pattern on hair microscopy. *T. violaceum* was the most commonly isolated fungus. Cure rates of 96 %, 88 %, and 84 % were achieved with griseofulvin (6 weeks), terbinafine (2 weeks), and fluconazole (6 weeks), respectively. Ten percent required prolonged therapy, in each group. The authors concluded that griseofulvin remains the drug of choice in the treatment of TC [80]. A retrospective review of 84 inner-city children in New York with tinea capitis was performed; they were primarily coloured with 60.6 % African-American, 28.2 % Hispanic, and 9.9 % Caucasian [13]. Treatment with a 4- to 6-week course of griseofulvin demonstrated greater success with the crushed tablets as compared to the suspension. Fifteen of the 'griseofulvin failures' achieved complete clearing by fluconazole in 5, terbinafine sprinkles in 7, and itraconazole in 3 [13].

In a randomised double-blind study, 176 children with *Trichophyton* tinea capitis were given 1, 2, or 4 weeks of terbinafine 3–6 mg/kg daily. Complete healing was achieved at 12 weeks after beginning therapy respectively in 42, 49 and 56 with the rate of…cure 52, etc rate of mycological cure was 52, 69, and 61 %. Healing increased nearly linearly from the second week of observation onward [16]. In another study, in 165 children in whom *M. canis* was the causative pathogen in tinea capitis, patients were randomised in a double-blind study and given 6, 8, 10, or 12 weeks of terbinafine (3–6 mg/kg daily) or 20 mg/kg griseofulvin. Complete healing with griseofulvin was achieved in 84 %, while with terbinafine there was a plateau in the 6-week group in 62 % [27]. Elewski and colleagues [41] describe two randomised blind studies in which griseofulvin suspension (10–20 mg/kg) was compared with a new terbinafine granulate (5–8 mg/kg) for the treatment of tinea capitis. Terbinafine granulate was shown to be significantly more effective against *Trichophyton*, while griseofulvin was more effective against Microsporum tinea capitis. In the United States, terbinafine granulate is FDA approved for use in children aged 4 and older. The recommended dosage is higher than that for the tablet form of the drug, however (125 mg/daily up to 25 kg, 187.5 mg/daily for 25–35 kg, and 250 mg/daily for patients >35 kg). The recommended treatment duration is 6 weeks. Most practitioners no longer perform routine blood tests for systemic therapy, unless treatment is prolonged beyond 6–8 weeks or other complicating factors are present. Complete blood count, liver and renal tests, as well as potassium can be monitored [77].

The azoles are also fungistatic and fungicidal depending on concentration [78, 79]. **Itraconazole** 3 mg/kg/day oral solution to 5 mg/kg/day capsules [79] for 4–6 weeks and **fluconazole** at 6–8 mg/kg/day for 6 weeks are comparable to griseofulvin; however they are not considered first-line therapy and often are not officially approved for tinea capitis by government regulations [77]. They have an advantage of availability in suspension; however they have a risk of drug interactions due to affinity for cytochrome P-450 enzymes,

Table 18.4 Reasons for treatment failure [96]

Poor adherence to treatment
Dose or duration of therapy inadequate
Dermatophyte resistant to drugs (very rare)
Reinfection from close contacts or fomites
Griseofulvin capsules (or tablets) appear to be more effective than liquid preparation

and gastrointestinal side effects, and should have monthly blood test [78, 79]. Ketoconazole is not recommended due to risk of hepatotoxicity [78].

Griseofulvin, fluconazole, and itraconazole secreted in large amounts in sweat reduce spores on the hair surface. Terbinafine which in contrast is not detectable in sweat is less effective in paediatric ectothrix hair infections than in endothrix infection [77].

Practice guidelines for the treatment of tinea capitis were issued from the European Society for Pediatric Dermatology in 2010 [75]. Griseofulvin was recommended as the treatment of choice due to efficacy for *Microsporum* as compared to terbinafine, and although terbinafine succeeds in *Trichophyton* infections with shorter treatment duration, griseofulvin has a lower cost [75, 79]. Similarly, meta-analysis in 2013 of randomised controlled trials between griseofulvin (6.25–12.5 mg/kg/day)×8 weeks and terbinafine 3.125–6.25 mg/kg/day×4 weeks did not show a significant difference in the overall efficacy [81]. However, for tinea capitis due to Microsporum spp., griseofulvin is superior ($p=0.04$), whereas terbinafine is superior for *Trichophyton* spp. infection ($p=0.04$) [81]. Failure to clear may be due to a variety of reasons (see Table 18.4).

Successful clearing was reported in 25 children with kerion celsi primarily due to *T. tonsurans*, with one month of terbinafine, and without the use of oral corticosteroids (prednisone 1 mg/kg/day for 1 week) as previously adopted by many in practice [82]. Oral antibiotics (24 %) and potent topical corticosteroids (20 %) were given to some, but all cases achieved equivalent clinical end points, regardless of adjuvant treatment, similar to Honig's study in 1994, although scaling and pruritus might diminish faster [83]. Concomitant bacteria (*Staphylococcus aureus* in 48 % and gram-negative bacteria in 18 %) can be recovered from kerion [84].

Complementary Topical Therapy and Measures of Hygiene

Antifungal shampoos, such as ketoconazole 2 %, selenium sulphide 2.5 %, zinc pyrithione, and the solution povidone iodine 4 %, decrease spore load and the shedding of anthroconidia [80]. They should be used 5 min two or three times weekly until the patient is clinically and mycologically cured [75]. A terbinafine solution 0.01 % completely killed arthroconidia of five *Trichophyton* species after an exposure time of 15–30 min.[79] Europeans recommend the addition of topical fungicidal cream/lotion to the lesions once daily for a week [78, 79]. Regular handwashing is thought to reduce the spread of dermatophyte infection. Also avoid sharing hairbrushes, combs, hats, towels, and articles of clothing to decrease fomite-borne transmission. Shaving of hair has been shown to increase cure rates in the past; however it can lead to peer group ridicule and ostracism and so is rarely adopted [77, 80]. The treatment may be stopped after the culture is negative or when hair regrowth is clinically apparent [79]. However if the culture is still positive in spite of clinical improvement, treatment should be continued for another month [79]. The benefit of long-term use of antifungal shampoos in the year post-therapy is controversial [85–87].

Treatment of Contacts

Ideally examination of siblings and classmates should be performed as they may be asymptomatic carriers, or also be infected [5, 54, 88]. At least carriers should use an antifungal shampoo. They are a reservoir for spread of tinea capitis and tinea corporis [79]. There is controversy as to whether siblings without clinical lesions should be treated orally in prevention. Two studies that followed carriers of anthropophilic dermatophytes showed 10–21 % became index patients, 42 % had persistent carriage, and 37 % became culture negative after 4 months [89, 90]. For these reasons, screening the social environment of index cases is important. If possible, all household members of an anthropophilic scalp ringworm patient should also be examined and screened with the hairbrush or toothbrush methods. Additionally, parents should be asked about other possibly infected classmates. It is proposed that students in the entire school be screened if more than two classmates are infected [33]. There is a high epidemic potential of *M. audouinii*, *T. tonsurans*, and *T. violaceum* [3, 6, 58, 89, 90].

Viable fungal spores have been isolated from the floor, chairs, clothing, beds, pillows, curtains, brushes, combs, scissors, and other shared facilities in the household. Consequently the washable items (e.g. bedding and textiles) should be laundered, carpets should be vacuum cleaned, and floors mopped with a strong disinfectant. Brushes and combs as well as other hair accessories should be disinfected by boiling them for 5 min [79]. Scissors may be placed in an instrument disinfectant, e.g. 5 min in a Mucocit-B drill bath (this alcohol-based product is designed for disinfecting dental drills) [79].

Recommendations are still lacking on reliable disinfection of contaminated surfaces that cannot be exposed to extreme heat (>60 °C), because disinfectants are not

tested arthroconidia [77]. Everything that can be bleached should be, and regular vacuuming can help reduce the accumulation of spores in the home. A recent study presented by Kunder and Moriello at the World Congress Veterinary Dermatology looked at the efficacy of various household products to kill dermatophyte spores. The four that worked best were Clorox Cleanup (Clorox Company), Formula 409 (Clorox Company), Lysol (Reckitt Benckiser), and Accel (Virox Technologies) [91]. Sterilisation of fomites, such as hairbrushes and combs, is recommended.

Prognosis

If the treatment is adequate, in general, the prognosis is good. There is a possibility of superinfection by bacteria, scarring with some permanent alopecia, and changes in skin colour [79]. There is potential for reinfection from fomites, asymptomatic carriers, and active cases, so we must attempt to reduce epidemics by establishing therapeutic guidelines and specific prevention measures.

Ongoing Research

What about polymerase chain reaction (PCR) as a sensitive diagnostic tool [92]? PCR identifies the DNA of the dermatophyte in the sample submitted; however it does not necessarily differentiate between colonisation and ongoing infection. Pre-culture medication will significantly reduce the sensitivity of culture but not of PCR tests [92]. The final diagnosis can be obtained within 1–2 days, compared to 8 days or more, permitting the initiation of appropriate treatment and infection control [92].

Currently PCR for dermatophyte identification is offered by Research Associates Laboratories (RAL) in Dallas, TX, USA, and Healthgene in Toronto, ON, Canada. A nested PCR protocol was used; however this is not possible with the single step PCR [91].

Molecular tools to study dermatophytic fungi allow the identification of the species as well as its genotyping and have 100 % specificity and sensitivity [92]. Such data facilitate the clinical–epidemiological monitoring of these mycoses and the identification of outbreaks [88].

T. tonsurans strains have striking phenotypical variation; however a low genetic polymorphism with the virulence genes CarbM14, Sub2, CER, and URE was detected in all [93]. The LAC gene was also found in all, and indicates the possible participation of melanin in the pathogenesis of these dermatophytes [93]. At the same time, different antifungal susceptibility can be studied through MIC values [88].

Fifty-seven *T. rubrum* cases had species identification by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis showing genetic diversity at 85.4 % [94].

Identification of dermatophytes by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry [95] is quick and can be used on 3-day-old cultures for species identification, as compared to morphological criteria and internal transcribed spacer sequencing (gold standard) [95].

Summation/Conclusion

Tinea capitis is a common paediatric infection, most particularly in children of colour. The anthropophilic dermatophytes are responsible for worldwide epidemics in cities, with increasing immigration and crowding, and often selectively thrive in the dense, thick tightly curled hairs of dark races. Zoophilic fungi present more commonly in rural settings, carried by cattle, cats and dogs, and exotic rodent pets. For years we have used Wood's light, which may help diagnose ectothrix infections, and now we can use dermoscopy on hairs, called trichoscopy, to identify comma-shaped and corkscrew broken hairs characteristic of tinea capitis. Direct microscopy of infected hairs may be helpful but time-consuming. Culture remains the gold standard and is positive in 85–98 %. The methods to obtain the culture are efficacious in descending order: cytobrush, hairbrush, toothbrush, culture swab, and last, scraping with a blade. Combined culture methods produce a higher yield. In the future, PCR may offer a rapid diagnostic test in 1–3 days. Therapy of tinea capitis is systemic, with adequate weight-based dosage of griseofulvin, terbinafine, and less commonly itraconazole or fluconazole over 4–8 weeks continued until clinical clearing and negative culture. A topical antifungal shampoo reduces dissemination of spores for the proband as well as other family members. Close contacts should be examined. Cleansing of the environment with bleach-based products, mechanical means, and washing potential fomites and clothing in boiling water are important for anthropophilic and zoophilic infections.

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Cutaneous Infections

19

Patricia A. Treadwell

Abstract

Promptly recognizing cutaneous infections can result in improved patient outcomes based on timely initiation of appropriate therapies. This chapter discusses some of the nuances associated with select cutaneous infections in skin of color, including clinical appearance, demographic distribution, and response to therapy.

Keywords

Impetigo • Molluscum contagiosum • MRSA • Pityriasis versicolor • Tinea corporis • Tinea capitis

Bacterial Infections of the Skin

Introduction

A superficial bacterial infection of the skin is termed impetigo. Folliculitis, furuncles, and carbuncles are diagnosed if the infection is focused around follicular openings, and based upon the depth of the infection.

Epidemiology

- **Increased incidence in summer**
- **MRSA increased in wrestlers**
- **Some populations of color may have more bacterial infections (e.g., black patients)**

The incidence of staphylococcal infections of the skin has been noted to be increased in blacks [1]. Impetigo is generally more common in the summer months related to disruptions of the skin barrier (bites and traumatic erosions). The exposed areas of the skin are most commonly affected. In the United States and in Japan, the most common etiologic agent is *Staphylococcus aureus* [2, 3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are more common in student athletes engaged in the sport of wrestling [4]. Cutaneous infections are more common among wrestlers because of the combination of skin abrasions and skin-to-skin contact.

Clinical Presentation

- **Folliculitis shows small pustules**
- **MRSA tends to form abscesses**
- **Impetigo is a bacterial infection of the skin presenting with flaccid bullae and crusting**
- **Erythema may be less notable in darker patients**

Impetigo is characterized by the formation of flaccid bullae which rupture easily. The serosanguineous fluid from inside can form a honey-colored crust. The bullae spread out from the initial lesion through self-inoculation in somewhat of a clustered pattern. Erythema will be less apparent in skin of color, but the clinical distribution and patterns will be similar (Fig. 19.1).

Two to 3 mm superficial pustules centered around follicular openings are noted in folliculitis. Folliculitis tends to be concentrated in occluded areas." Hot tub folliculitis" is a

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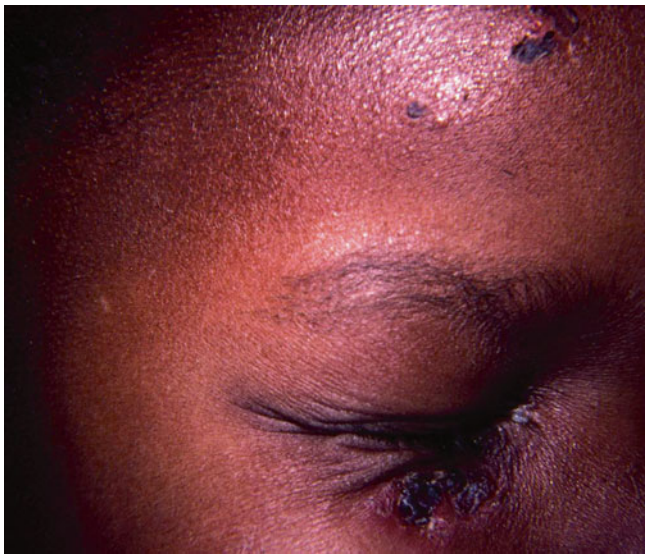

Fig. 19.1 Clustered crusts of lower eyelid and forehead in impetigo. One pustule is also noted on the forehead

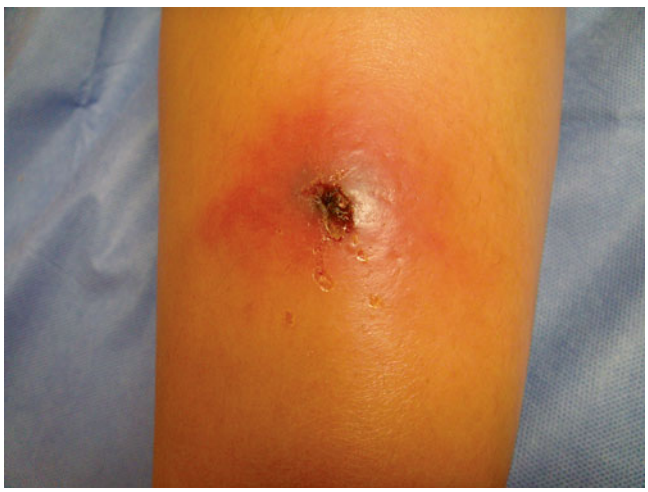

Fig. 19.2 Carbuncle due to MRSA with a central area of fluctuance

particular type of folliculitis which occurs following being seated in a hot tub. Typically, the causative organism in "hot tub folliculitis" will be *Pseudomonas aeruginosa* [5, 6]. The pustules may be arranged in a linear pattern corresponding to the hot tub water levels or concentrated in areas of occlusion, such as under a tight bathing suit.

Skin and soft tissue infections due to Methicillin-resistant *Staphylococcus aureus* (MRSA) tend to form abscesses. These lesions are termed furuncles (one hair follicle involved) or carbuncles (more than one hair follicle involved). The lesions are erythematous and are often painful. A purulent cavity can develop which will result in an area of fluctuance (Fig. 19.2).

Clinical Presentation

- **Flaccid bullae rupture easily**
- **Folliculitis shows small pustules**
- **MRSA tends to form abscesses**
- **Limited areas of impetigo can be treated topically**
- **Institute measures in the household to limit spread**

Treatment

- **Treatment of impetigo can be accomplished with oral or topical anti-infectives.**
- **Incision and drainage, bleach baths, and decolonization using nasal mupirocin are all potential adjunctive therapies.**

Impetigo which is confined to a limited area can be treated topically with mupirocin or retapamulin twice daily for 5–7 days. If the lesions are more extensive, oral antibiotics are prescribed for 7–10 days. The choice of the antibiotic depends on the particular organisms and sensitivities of the region in which a patient lives.

Folliculitis can be treated with antibacterial soaps, avoidance of occlusion, and, if needed, topical antibiotics. Recurrence of "hot tub folliculitis" can also be minimized by avoidance of the offending hot tub, by increasing the chlorination of the hot tub water, and/or by changing the water frequently [7]. In addition, topical clindamycin or mupirocin may help speed resolution in this variety of folliculitis.

MRSA furuncles and carbuncles are best treated with incision and drainage (I&D) [8]. Systemic antibiotics may or may not be necessary depending on the ability to adequately drain the lesions and depending on the host's immune status. When more than one individual in a household is affected, instructions are provided to limit spread among household members, including good hand washing, keep draining wounds covered, and avoid reusing or sharing personal items [2]. Student athletes should be instructed to clean any shared equipment [4]. After the active infection is treated, decolonization with nasal mupirocin and bleach baths can be attempted [9].

Prognosis

Gutierrez et al. [1] found that black children had a higher risk for hospitalization for bacterial skin infections than white or Hispanic children. In immunocompetent children, superficial bacterial infections have a good prognosis and will generally resolve completely.

MRSA infections which spread systemically can be associated with serious complications.

Ongoing Research

Periodic microbiologic cultures in communities will assist in data collection regarding regional antibiotic sensitivities.

Conclusion

Proper diagnosis of bacterial infections of the skin will allow practitioners to initiate therapy promptly and improve patient outcomes.

Tinea Corporis

Introduction

Tinea corporis lesions result from an inoculation of dermatophyte organisms into the skin when there has been a disruption of the skin barrier. Dermatophytes are fungi that digest keratin and therefore can live in keratinized skin and scalp hairs at or above the beginning of keratinization in Adamson's fringe.

Epidemiology

- **Not increased in skin of color**
- ***Trichophyton rubrum* most common cause worldwide**
- **Incidence is increased in wrestlers**
- **Tinea corporis is a ubiquitous dermatophyte infection**
- **Spread occurs through close contacts and fomites**

Tinea corporis occurs with the same incidence in children of color as the general population. Tinea corporis is seen more frequently in the summer when there tends to be a higher incidence of insect bites, cuts, and erosions. Spread can occur with skin-to-skin contact, from tinea capitis or from fomites in households, or on common play surfaces. Tinea corporis is another one of the infections which is more common in children who engage in the sport of wrestling. The most common organism which causes dermatophytosis worldwide is *Trichophyton rubrum* [10, 11]. Specifically for tinea corporis, the most common causative organism in North America is also *Trichophyton rubrum*. In the United States and Mexico, other causes are *Trichophyton mentagrophytes, Trichophyton tonsurans*, *Microsporum canis*, and *Epidermophyton floccosum.*

Clinical Presentation

- **May develop into pustules and/or vesicles**
- **Seen most often on exposed areas**

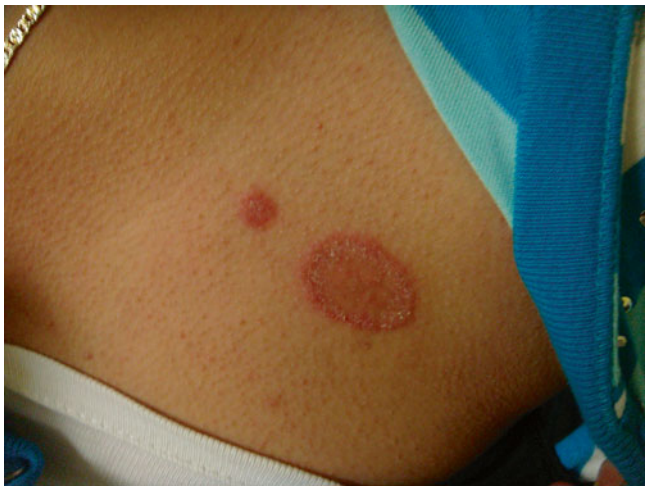

Fig. 19.3 Tinea corporis in a Hispanic adolescent

- **Annular lesions with a collarette of scale are typical.**
- **Involvement of the hair can occur in areas of dense body hair.**

Lesions of tinea corporis are typically circular or annular erythematous raised lesions with scale (Fig. 19.3). More significant cases may develop a vesicular or pustular component. A deeper follicular component may be noted in areas of dense body hair, e.g., Majocchi's granuloma. Tinea corporis lesions are most often located on exposed areas of the body. Pruritus may be noted.

Treatment

- **Use topical antifungal agents for 48–96 h after clinically resolved**
- **Topical antifungals can be used to clear tinea corporis**
- **Oral antifungals can be required in specific settings, including hair involvement**

Topical antifungals (azoles or allylamines) are applied to the lesions and to 2 cm of surrounding skin [10] twice daily for approximately 2 weeks continuing for 48–96 h after lesions appear resolved. If the lesions are more infiltrated, are located in an area with increased hair (eyelashes, beard areas in adolescents, legs or arms in some patients), or are very widespread, systemic antifungal therapy may be needed.

Prognosis

The lesions may eventually resolve spontaneously; however, treatment is recommended to hasten resolution and to avoid continued self-inoculation. In skin of color, postinflammatory dyspigmentation may present unique challenges (Fig. 19.4). Patients who are diagnosed with tinea corporis

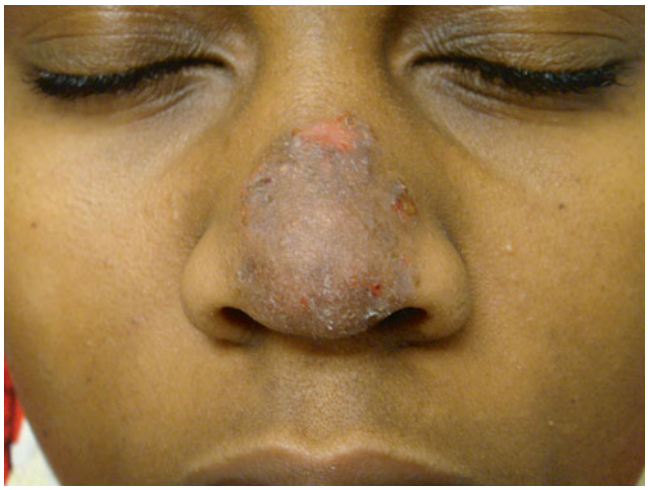

Fig. 19.4 Postinflammatory hyperpigmentation noted in a healing lesion of tinea corporis

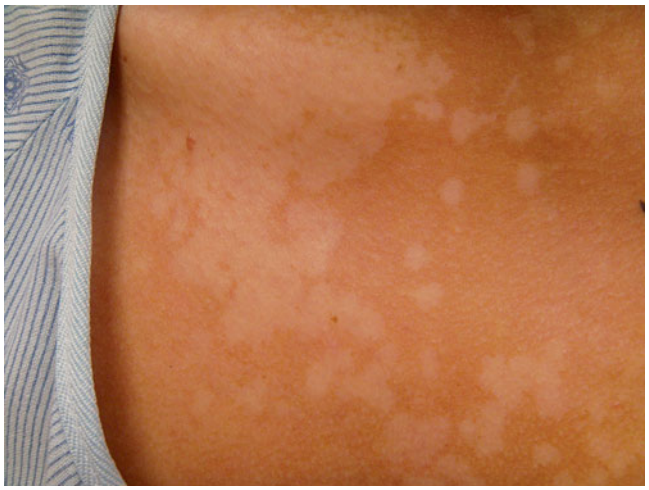

Fig. 19.5 Pityriasis versicolor; hypopigmented scaly patches on the chest

should be cautioned to avoid contact with individuals, fomites, or pets that may carry the organisms to decrease the incidence of reinfection. Topical corticosteroids should be avoided as they may cause enlargement of the lesion and poor response to antifungals.

Ongoing Research

Ongoing studies to determine the etiologic agents of tinea corporis provide useful information regarding the incidence of each organism and can direct therapeutic options.

Conclusion

Tinea corporis is a benign cutaneous infection which clears with azole antifungals; however, in skin of color the postinflammatory changes can cause parental concern. Reduction in transmission of disease is important in households to contain the spread of the infection.

Pityriasis Versicolor

Introduction

Pityriasis versicolor aka tinea versicolor (TV) is a superficial yeast infection of the skin. The causative organism is the yeast form of the dimorphic fungus of the *Malassezia* genus. The organisms have also been known as *Pityrosporum orbiculare* or *ovale*. The organism is lipophilic and tends to be concentrated in areas with increased sebaceous glands.

Epidemiology

- **No consensus as to whether incidence is increased in skin of color**
- **Increased incidence in summer and in tropical climates**
- **Increased in pregnancy, diabetes, and immunosuppression**
- **Tinea versicolor is a common cutaneous yeast overgrowth**

Evidence regarding whether the incidence is different in skin of color is not conclusive [12]. However, it is clear that the pigmentary changes can alter the clinical presentation. The incidence of pityriasis versicolor is increased in the summer, in tropical climates, during pregnancy, and in association with diabetes and immunosuppression.

Clinical Presentation

- **Lesions have powdery scale**
- **Facial involvement noted in prepubertal children**
- **Scale may be hypopigmented or hyperpigmented**
- **Hypopigmented annular plaques of the head, upper chest, and back are typical for Black or African-American patients.**
- **Hyperpigmented to pink plaques with minimal scale are noted in many patients with Fitzpatrick phototypes I–V**

TV lesions are macules with powdery scale which may coalesce into patches. The usual locations are the upper back and upper chest (Fig. 19.5). However, in prepubertal children, the lesions may be present on the face [10]. The lesions may be hypopigmented or have a brownish coloration. In more richly pigmented skin, the lesions may have a follicular

orientation [13] and be more obviously hypopigmented. The *Malassezia* organism is difficult to culture; thus diagnosis is made based on the clinical appearance and/or potassium hydroxide preparations [14]. Wood's lamp examination in some instances shows pale yellow fluorescence [10]. Biopsy of pityriasis versicolor in skin of color shows a thicker stratum corneum, more tonofilaments in the granulosum, and more sequestered melanosomes [12].

Treatment

Treat with topical imidazoles

- **Can use topical lotion or shampoos**
- **Extensive cases can be treated with oral antifungal agents**
- **Topical imidazoles aid in clearance**
- **Shampoos or oral medications are possible alternatives**

Limited areas of pityriasis versicolor can be treated with topical imidazoles. More extensive cases are treated with topical zinc pyrithione shampoo, selenium sulfide lotion [15], or ketoconazole shampoo [12]. Alternate treatments for the most extensive cases include oral ketoconazole, itraconazole, or fluconazole [16].

Prognosis

Pityriasis versicolor is a superficial infection which is not associated with any systemic symptoms other than occasional pruritus. The infection may require retreatment each year. The dyspigmentation may not resolve for months even after adequate treatment.

Ongoing Research

Since the pityriasis versicolor organism is difficult to culture, it is challenging to document epidemiologic pattern shifts or changing sensitivities [16].

Conclusion

Pityriasis versicolor is an often persistent superficial infection which may require yearly retreatment.

Tinea Capitis

Introduction

The term tinea capitis is used to describe a dermatophyte infection of the scalp hairs. Tinea capitis is the most common superficial fungal infection in North America [10].

Epidemiology

Increased in African-American children

- ***Trichophyton tonsurans* most common etiologic agent in United States, Canada, Ireland, and the United Kingdom**
- ***Microsporum canis* most common etiologic agent in South America, Europe, the Middle East, Asia, and Australia**

The most common causative organism in the United States, Canada, Ireland, and the United Kingdom is *Trichophyton tonsurans* [10, 17]. *Microsporum canis* continues to be the most common etiologic agent in South America, Europe, the Middle East, Asia, and Australia [10]. Children are more often affected with tinea capitis when compared to adults. Children aged 3–9 have the highest incidence. The incidence of tinea capitis is increased in African-American children [17]. The increased incidence has been noted to be independent of shampooing practices and use of hair grease or oils [18].

Clinical Presentation

- **Patches of alopecia**
- **Occipital lymphadenopathy may be present**
- **Kerion may develop**

Clinical features of tinea capitis include patchy alopecia with scale often with lymphadenopathy (Fig. 19.6b). Some children may present with only diffuse seborrheic-like scale or crusted lesions [10]. Patients with a more intense inflammatory response to the infection may develop vesiculopustular lesions or even a kerion. Kerions occur as the result of a significant inflammatory response to the dermatophyte by the host. Kerions are characterized by alopecia, purulence, crusting, pain, and edema. After treatment is started, a dermatophytid or "id' reaction can be seen. This reaction is an autosensitization dermatitis not a true drug reaction characterized by fine papules noted especially on the neck, trunk, extremities, and face (Fig. 19.6a).

A potassium hydroxide preparation can be utilized to demonstrate spores within (endothrix) or surrounding (ectothrix) the infected hairs. Wood's lamp exam will show green fluorescence with ectothrix organisms such as *Microsporum canis* and *Microsporum audouinii* [10]. Wood's lamp examination will be negative for endothrix organisms such as *Trichophyton tonsurans* and *Trichophyton violaceum.* Fungal culture can be useful in confirming the diagnosis and identifying the specific causative organism.

Treatment

- **Tinea capitis requires systemic therapy**
- **Use shampoo as adjunct therapy**
- **Different organisms have a varied response to oral medications**

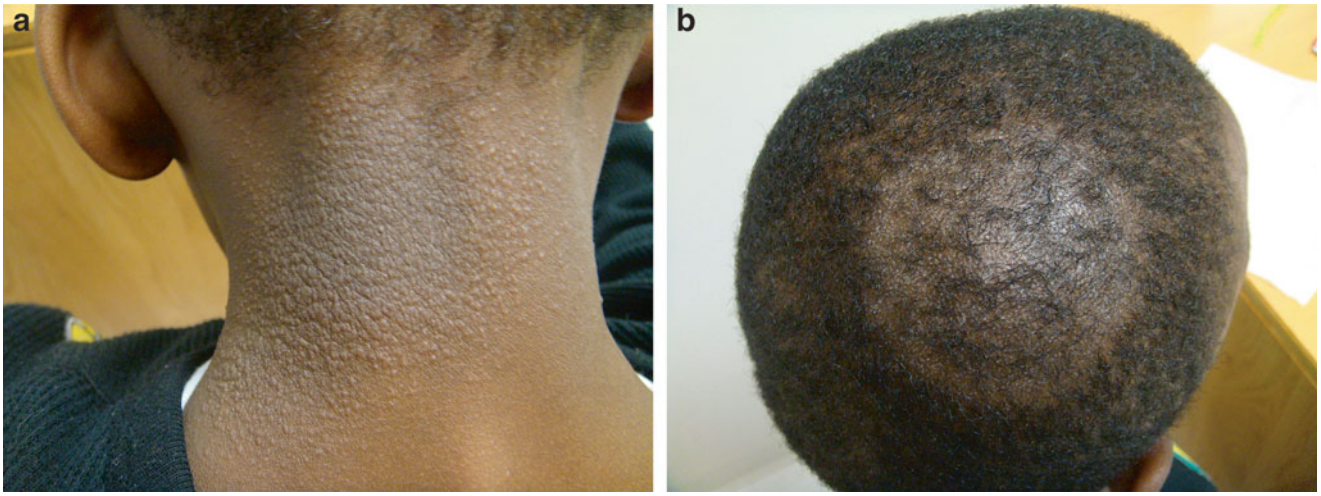

Fig. 19.6 (**a**) "Id reaction" papules on the neck of a patient with tinea capitis on griseofulvin. (**b**) Healing tinea capitis in the same patient with no erythema and minimal scale

Tinea capitis infections require oral anti-mycotics. They are not sufficiently treated by using topical agents alone [19]. Griseofulvin is still the first-line treatment. It is prescribed at a dose of 15–25 mg/kg/day for 6–8 weeks. Weekly selenium sulfide shampoo or ketoconazole shampoo (both sporicidal) or ciclopirox shampoo is used as an adjunct therapy. A short course of systemic corticosteroids may be necessary for kerions. If treatment with griseofulvin is not successful, fluconazole (6 mg/kg/day for 20 days), itraconazole (3–5 mg/kg/day for 4–6 weeks), or terbinafine (125 mg/day for 20–40 kg child for 2–4 weeks) can be prescribed. Tinea capitis due to *Microsporum canis* has a slower response to terbinafine than to griseofulvin [20, 21]. Systemic antibiotics are needed only when a frank secondary bacterial infection occurs.

Children with tinea capitis should be instructed to avoid head-to-head contact with other children and avoid sharing combs, brushes, hats, head gear, hair ornaments, and pillowcases [10].

Prognosis

Tinea capitis is generally responsive to treatment. Hair typically will regrow, but scarring alopecia may be associated with a diagnosis of a kerion because of the intense inflammation which may damage the hair follicles.

Ongoing Research

Causative organisms for tinea capitis are studied on an ongoing basis to determine etiologic patterns. Research continues to compare treatment options and provide guidelines for proper therapy. Specific reasons for the increased incidence in African-American children have not yet been delineated and require further study.

Conclusion

It is important to identify and treat tinea capitis promptly, specifically in order to avoid persistent scarring alopecia.

Molluscum Contagiosum

Introduction

Molluscum contagiosum is a cutaneous infection caused by poxvirus [22].

Epidemiology

- **No increase in skin of color**
- **Increased incidence in wrestlers**
- **Increased incidence in immunosuppression**

No difference in the incidence of molluscum contagiosum is noted in children of color. Molluscum contagiosum is an additional cutaneous infection which is increased in children engaged in the sport of wrestling. The incidence is also increased in the face of immunosuppression.

Clinical Presentation

Molluscum contagiosum lesions are typically 2–5 mm in diameter. They are smooth dome-shaped papules which are

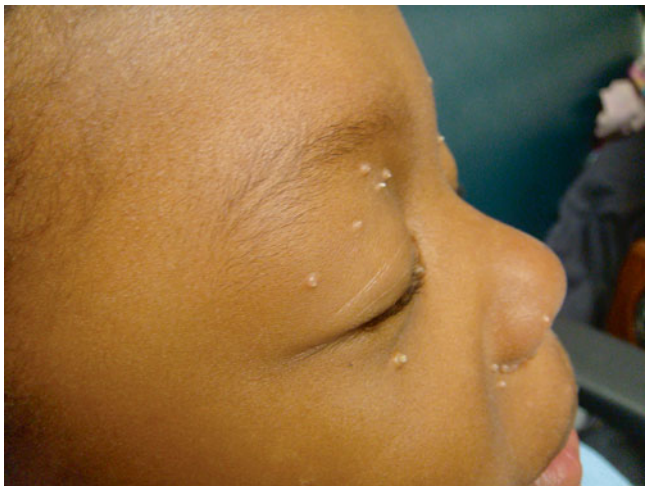

Fig. 19.7 Wart-like projections on molluscum contagiosum lesions

skin colored and occur on any skin surface, but are especially found in the axillae and arms and legs. They can spread through self-inoculation, producing clusters of papules. In some cases, the lesions may develop wart-like projections (Fig. 19.7). In approximately 10 % of patient, molluscum dermatitis may be seen. Molluscum dermatitis is characterized by an eczematous eruption centered around a molluscum lesion.

Treatment

- **Destructive treatments are cantharidin and cryosurgery**
- **Imiquimod upregulates cytokines**
- **Postinflammatory hyperpigmentation may occur especially with destructive treatment in children of color**

Since the causative organism is a poxvirus, the lesions may heal with a "pock-like" scar whether they resolve spontaneously or are treated.

A variety of treatments are available for molluscum contagiosum, including cantharidin curettage, cryosurgery, imiquimod (effect through upregulation of cytokines), retinoids, cimetidine, salicylic acid, and cidofovir [22]. Chen et al. [23] concluded that "No evidence-based consensus has been reached on best treatments for molluscum contagiosum in immunocompetent patients". The choices are tailored to each particular patient's needs. In skin of color, treatment with cryosurgery and cantharidin can result in dyspigmentation and scarring. The parents and patients should be made aware of the potential pigmentary changes following treatment. Therapies which minimize dyspigmentation should be utilized.

Wrestlers may request more aggressive treatment in order to be cleared to get back to competition.

The molluscum dermatitis can be treated with topical corticosteroids in addition to treating the molluscum contagiosum.

Prognosis

Each individual lesion can resolve spontaneously after a few months. However, therapy is recommended for lesions which are multiplying at a worrisome rate or are widespread [22].

Ongoing Research

Studies to identify the most effective therapies for molluscum contagiosum are ongoing.

Conclusion

Molluscum contagiosum lesions are not associated with systemic complications, but can be treated to avoid continued self-inoculation and decrease the incidence of dermatitis.

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Molluscum Contagiosum, Viral Warts, and Tinea Versicolor

20

Yuin-Chew Chan

Abstract

Molluscum contagiosum and viral warts are common viral infections in children. They are benign infections that often resolve spontaneously in healthy children. Treatment is often sought to reduce cutaneous dissemination, social stigma and spread to close contacts. Painless topical therapy is often preferred for younger children. Older children may be able to tolerate more aggressive therapeutic modalities. A combination of treatment options is often used for recalcitrant viral warts and molluscum. Tinea (pityriasis) versicolor usually occurs in adolescents. It responds well to treatment with topical antifungal agents, but recurrence is common.

Keywords

Human papilloma virus • Molluscum contagiosum • Pityriasis versicolor • Malassezia

Molluscum Contagiosum

Introduction

The molluscum contagiosum virus (MCV), a DNA poxvirus, causes this common benign skin infection. Restrictive endonuclease analysis of the genomes of isolates has identified MCV types I to IV. Infections are predominantly caused by MCV type I in childhood (ages 1–15 years) and, less commonly, type II, which is generally seen in teenagers who are sexually active.

The incubation period ranges from 2 weeks to 6 months. The virus infects the epidermis only and replicates in the cytoplasm of epithelial cells.

Cell-mediated immunity plays a key role in controlling the infection. Children with HIV infection, who are immunocompromised or on immunosuppressive drugs, have more widespread lesions.

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Epidemiology

- **Molluscum contagiosum occurs worldwide, but is more common in tropical, humid areas**
- **Spread by contact with infected skin and fomites**
- **Patients with atopic dermatitis have more recalcitrant infections with higher relapse rates**

This infection occurs throughout the world. It is more prevalent in tropical areas, in warm humid climates, and in crowded areas. It occurs most commonly in children.

Infection is rare in infants, although congenital cases have been reported [1].

An association with swimming pool use and sharing of bath sponges and towels with an infected person has been reported [2, 3]. The virus is most likely spread by contact with infected skin or fomites like towels, kick boards, clothing, or toys. Viral spread through water has been suggested but not proven.

Molluscum contagiosum appears to be associated with atopic dermatitis, but a recent study suggests otherwise [4]. However, patients with atopic dermatitis, once infected with molluscum contagiosum, tend to experience more recalcitrant infection with a higher relapse rate [5].

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Fig. 20.1 Pearly papules of molluscum contagiosum on the face and upper lip

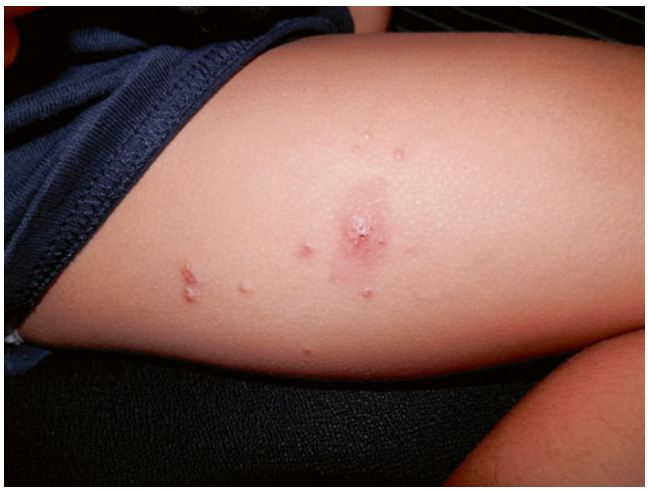

Fig. 20.3 Molluscum dermatitis on the thigh

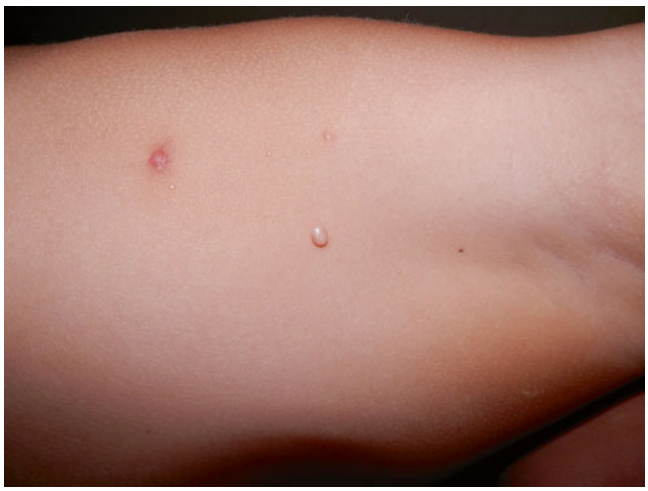

Fig. 20.2 Giant molluscum contagiosum in the axilla

Clinical Presentation

- **Pearly papules with central umbilication is characteristic**
- **Autoinoculation caused by scratching may result in linear spread**
- **Molluscum dermatitis heralds regression and does not require treatment unless it causes discomfort or pruritus**

Skin lesions consist of grouped dome-shaped pearly papules (Fig. 20.1). Active lesions often contain central white plugs. Central umbilication may be seen and is a pathognomonic sign. Giant molluscum that contains several clumps of molluscum bodies presents as a pink or pale-colored nodule (Fig. 20.2). Lesions may appear on any part of the body, most commonly on the trunk, axillae, arms, groins, and thighs. The palms and soles are hardly ever affected. Children with atopic dermatitis or HIV infection or who are immunocompromised (e.g., transplant-related immunosuppression) may develop numerous lesions. Autoinoculation caused by scratching or minor skin trauma may result in the papules spreading in a linear pattern.

Children often develop hypersensitivity reactions to the MCV that manifest as eczematous patches surrounding the molluscum papules (Fig. 20.3). These eruptions are often referred to as molluscum dermatitis. In addition, the hypersensitivity reaction can sometimes occur at distant sites (i.e., the id reaction). These eczematous reactions are often asymptomatic or slightly pruritic. Some authors believe that these id reactions represent an immunologically mediated host response to the virus and herald the onset of regression [6]. These reactions do not require any treatment other than emollients. However, in symptomatic patients, a short course of topical corticosteroids is helpful.

Secondary bacterial infection is an uncommon complication.

Management

- **Molluscum contagiosum resolves spontaneously over several months to years**
- **In younger children, relatively painless treatments like topical tretinoin, topical salicylic acid, and imiquimod cream are good options**
- **In older children, curettage, cryotherapy, and cantharidin are effective options**

The diagnosis of molluscum is usually made clinically. Differential diagnoses include plane warts, milia, and papular eczema. Rarely coccidioidomycosis or other fungal infections of the immunocompromised host can mimic molluscum.

In uncertain cases, the presence of intracytoplasmic eosinophilic inclusion bodies, also known as molluscum bodies, on histologic examination of a skin biopsy will clinch the diagnosis.

In healthy children, molluscum contagiosum heals spontaneously within months to several years. However, parents often request for treatment as it may help to reduce autoinoculation and transmission to close contacts and improve clinical appearance.

A recent Cochrane review found that no single intervention had been shown to be convincingly effective in the treatment of molluscum contagiosum [7].

A prospective randomized study compared curettage, cantharidin, combination of salicylic acid and lactic acid, and imiquimod for molluscum contagiosum in children [8]. Curettage was found to be the most efficacious treatment and had the lowest rate of side effects. Cantharidin was a useful alternative office procedure, but had moderate complications due to blisters and necessitated more visits. The salicylic acid/lactic acid combination was effective but too irritating for children. Topical imiquimod was promising, but expensive, and the optimum treatment schedule had not yet been determined.

The infected areas should be covered with clothing or bandage and good hand hygiene should be practiced to prevent spreading to others, especially during contact sports. Personal items like towels and clothing should not be shared. Bath sponges should be avoided due to risk of autoinoculation.

Office Treatment

Cantharidin 0.7 % in flexible collodion is a vesicant that should be carefully applied to the molluscum contagiosum papules with a wooden stick and allowed to dry thoroughly. It is a quick, painless, and effective treatment, but causes blisters on the sites of application. It should be applied with great caution to flexural areas, like the axillae, cubital, and popliteal fossae, because of the risk of extensive blistering. The extent of blistering and discomfort varies in different individuals, and hence the initial treatment should be done conservatively. The blistering is limited to the epidermis, and does not scar unless there is secondary infection [9–12]. Several treatment sessions are usually required for complete clearance. Unfortunately, cantharidin is not readily available in some countries.

Curettage is very effective in removing molluscum contagiosum. However, it is painful, time-consuming, and best done in a cooperative child who has received adequate topical anesthesia, e.g., with eutectic mixture of lidocaine and prilocaine 2.5 % cream. There is a risk of methemoglobinemia with usage over large surface areas, and the prescribing guide should be consulted for maximum volume that can be used in one session based on the child's weight. For children with multiple lesions, several treatment sessions are usually required for complete clearance [13, 14].

Cryotherapy is an effective procedure. Light freezing of the lesion and minimal icing of the surrounding skin usually suffices. However, it is painful and often induces hypopigmentation in children with skin of color that may persist for weeks. Topical anesthesia is often required in younger children.

Trichloroacetic acid 12 % solution has been reported to be an effective and safe therapy for facial molluscum contagiosum in children [15].

Home Treatment

Topical keratolytic agents like tretinoin (up to 0.1 %) and salicylic acid (up to 17 %) can be applied to the papules on alternate days until an inflammatory response is produced [16].

Imiquimod 5 % cream, a toll-like receptor 7 agonist, induces alpha-interferon and cytokines upon topical application. It is applied 3–5 days a week to molluscum lesions until they become inflamed. It is slow acting and expensive but effective, painless, and a good option in young children with numerous small lesions or lesions on the face [17, 18].

Topical potassium hydroxide 10 % aqueous solution, a strong alkali, can be applied daily to molluscum lesions until complete resolution. It has been found to be effective and safe when used at a lower concentration of 5 % on the face of children. It is an inexpensive treatment [19–21].

Prognosis

The prognosis is very good. Molluscum contagiosum is a self-limiting infection in healthy children. Spontaneous resolution may take up to several years. Most of the lesions resolve without scarring, although some may leave slightly depressed scars.

Ongoing Research

Further research is required to better characterize MCV viability in swimming pools.

Conclusion

Molluscum contagiosum is a common viral infection in children. It usually resolves spontaneously, but treatment is often sought to reduce cutaneous dissemination and social stigma. For younger children, relatively painless treatments like cantharidin, topical keratolytics, and imiquimod are good options. For older children and adolescents, curettage, cryotherapy, and cantharidin are effective options.

Viral Warts

Introduction

Warts are caused by the human papillomavirus (HPV), which is a double-stranded DNA virus. More than 100 types of HPV have been identified [22]. HPV 1, 2, 27, and 57 are the most prevalent HPV types found in cutaneous warts in the general population. Warts caused by HPV 1 have a distinct clinical profile, being related to children aged less than 12 years, plantar location, duration less than 6 months, and to patients with less than 4 warts [23].

Warts can affect any area on the skin and mucosa. The HPV virus infects the epithelium only, and systemic dissemination does not occur.

HPV is spread by direct skin contact or indirectly by contact with contaminated surfaces. Autoinoculation may occur, causing cutaneous dissemination. The incubation period for HPV usually ranges from 1 to 6 months, but may be as long as 2 years.

Epidemiology

- **Prevalence of warts among children is between 22 and 33 %.**
- **An increased risk of warts is found in children with a family history of warts.**
- **Warts spontaneously regress in up to half of children within 2 years.**

Warts are uncommon in infancy and early childhood, increase in incidence among school-aged children, and peak at 12–16 years [24]. The prevalence of warts among primary schoolchildren is reported to be 22–33 % [25, 26]. In the USA, warts are more common in white than black patients [27].

An increased risk of the presence of warts was found in children with a family member with warts, and in children where there was a high prevalence of warts in the school class [25]. The use of public swimming pools has been associated with a higher risk of infection [28].

Forty to fifty percent of children with warts have been found to be free of warts within 1–2 years [29, 30].

Clinical Features

- **Clinical subtypes include common warts, filiform warts, plantar warts, plane warts, and anogenital warts.**
- **Filiform warts are usually seen on the face.**

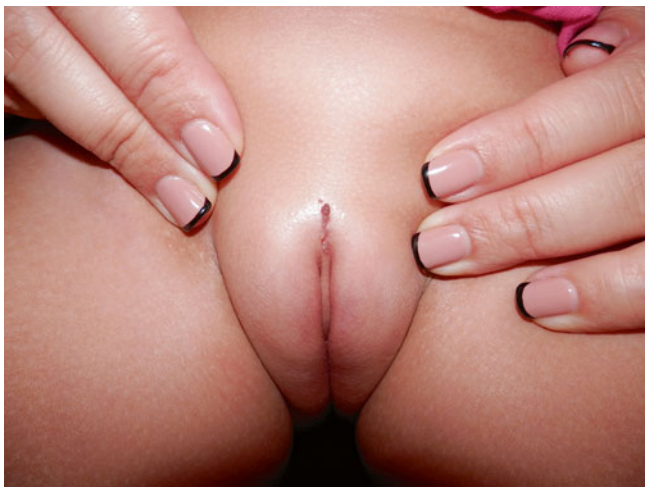

Fig. 20.4 Viral warts in genital area

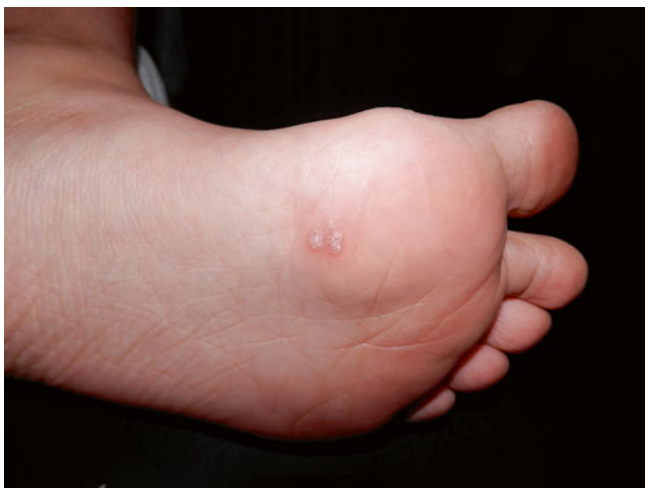

Fig. 20.5 Plantar warts

- **Plane warts are flat-topped and flesh-colored papules that may koebnerize.**

Common warts (verruca vulgaris) appear as hyperkeratotic papules with a rough, irregular surface. They can occur on any part of the body but are seen most commonly on the hands and knees (Fig. 20.4).

Filiform warts are long and narrow growths, usually seen on the face around the lips, eyelids, or nares.

Plantar warts (myrmecia) begin as papules and progress to well-demarcated round lesions with a rough keratotic surface (Fig. 20.5). They grow deep and may be painful. Occasionally, they are covered by calloused skin; paring this away will reveal the thrombosed capillaries appearing as black dots.

Plane warts (verruca plana) are slightly elevated, flat-topped, smooth, and flesh-colored papules. The face, dorsum of hands, and shins are the most common areas affected. These warts often exhibit the Köebner phenomenon.

Anogenital warts rarely occur in childhood. They appear as clusters of papillomatous lesions. Sexual abuse is a concern, but it is uncommon. The infection more often results from virus inoculation through perinatal transmission, autoinoculation from another body site, and infection from other family members and caregivers [31, 32].

Epidermodysplasia verruciformis is a rare inherited autosomal recessive disorder characterized by chronic HPV infection. Mutations in the EVER1 and EVER2 genes result in defective cell-mediated immunity. Warts usually appear in childhood on the sun-exposed areas. The lesions may appear like plane warts and resemble seborrheic keratoses or tinea versicolor. They tend to persist and may develop into squamous cell carcinoma in early to mid adulthood.

Management

- **Forty to fifty percent of warts in children resolve spontaneously within 2 years**
- **Salicylic acid is a cost-effective treatment for warts**
- **Regardless of the treatment used, warts may recur due to normal-appearing perilesional skin harboring HPV**

The diagnosis of warts is often made on clinical findings. Paring of warts may reveal minute black dots, which represent thrombosed capillaries. A skin biopsy can be considered if the diagnosis is in doubt.

Multiple modalities are available for the treatment of warts, but none is uniformly effective [33]. For children, it is appropriate to begin treatment with the least painful methods. The more invasive procedures should be reserved for refractory warts.

Home Treatment

Salicylic acid has a proven therapeutic effect in the treatment of nongenital cutaneous warts. Compared to placebo, it significantly increased the chance of clearance of warts at all sites [34]. It is cheap, readily available without a prescription and can be applied at home. It is probably the most cost-effective treatment for warts to date. Salicylic acid should be avoided on the face and intertriginous and anogenital areas as it may cause severe irritation and erosions in these areas.

Imiquimod is an immune response modifier that has been successfully used for the treatment of common warts [35, 36]. It can be applied to nongenital cutaneous warts once or twice daily and to anogenital warts once every other day. Once the warts or the surrounding skin become inflamed, imiquimod can be temporarily discontinued, and then resumed when the inflammation settles.

Tretinoin cream has been used for the treatment of viral warts. It is probably the most effective for facial and plane warts. Sixteen out of 20 children with extensive warts who were given oral etretinate 1 mg/kg daily up to 3 months showed complete regression of the disease without relapse [37]. The use of systemic retinoids may be considered in children with widespread warts, e.g., epidermodysplasia verruciformis.

5-Fluorouracil (5-FU) is a chemotherapeutic agent that has been reported to be safe and effective in treating warts in children [38]. It is thought to work by interfering with DNA and RNA synthesis. The 5 % 5-FU cream can be applied once daily. Adverse reactions include erythema, ulceration, and hypopigmentation.

Contact sensitizers like squaric acid and dinitrochlorobenzene have been shown to be effective and safe topical immunotherapies for warts in children. They offer an alternative therapeutic option for patients with multiple recalcitrant warts. Their main side effect is allergic contact dermatitis, which may cause blistering and secondary spread in the more severe cases [39–41].

Zinc is an immune modulator that has been shown to be effective in the treatment of children with recalcitrant warts in two randomized placebo-controlled trials done in the Middle East [42, 43]. The majority of the children in the trials had low zinc levels. They were given oral zinc sulfate at a dose of 10 mg/kg daily up to 600 mg/day. The most common side effects were nausea and mild epigastric pain.

Office Treatment

Cantharidin can be applied topically to warts in the clinic and washed off after several hours. It causes localized blistering within 1–2 days. For plantar warts, a combination compound of cantharidin 1 %, podophyllotoxin 5 %, and salicylic acid 30 % is effective and safe [44, 45]. However, patients should be warned that the compound can cause significant blistering and severe pain, and the first treatment should be done conservatively.

Liquid nitrogen (−196 °C) can be applied using a cotton bud applicator or cryospray to the wart and a 1–2 mm rim of normal skin tissue around the wart. It is repeated every 2 weeks for approximately 3 months, as required [46]. It is painful and may cause blistering, hypopigmentation, or scarring after treatment. There is a risk of keloid induction with deep cryotherapy over the chest. Pigmentary alteration, especially hypopigmentation, may occur in dark patients, including blacks, dark Asians, and Hispanics. Cryotherapy must be used with caution on the sides of fingers to avoid injury to underlying structures and nerves. Cryotherapy can rarely result in a central clearing with an annular recurrence of the wart surrounding the treated area ("doughnut wart"). Cure rates ranging from 43 to 83 % have been reported. Wart clearance may be achieved through necrotic destruction of

viral infected keratinocytes or by inducing local inflammation that triggers a cell-mediated immune response. Paring the wart, in addition to two freeze–thaw cycles, has been a valuable adjunct to cryosurgery for plantar warts [47].

The carbon dioxide laser produces nonselective tissue destruction. Wounds heal by secondary intention in several weeks. It is a therapeutic option for recalcitrant warts in children [48]. Local anesthesia is required and potential side effects include pain, infection, and scarring.

The pulsed dye laser targets the wart microvasculature. It appears to be an effective and safe alternative therapy of recalcitrant warts in children [49, 50]. Compared to the carbon dioxide laser, it is less painful and has a lower risk of scarring, but requires more treatment sessions.

Surgical treatment is very effective in treating older children with a few viral warts, especially filiform and common warts. These warts can be snipped, curettaged, or shaved away, followed by electrocautery of the bases. These surgical procedures carry risks of scarring, keloid formation, and dyspigmentation.

Prognosis

Forty to fifty percent of warts in children resolve spontaneously within 2 years. When warts resolve spontaneously, no scarring is seen. However, scarring can occur as a result of the more invasive treatment methods, e.g., carbon dioxide laser and surgical treatment. Periungual or subungual warts may cause permanent nail dystrophy.

Treatment failures and wart recurrences are common, more so among immunocompromised patients. Normal-appearing perilesional skin may harbor HPV, which helps to explain recurrences.

Ongoing Research

Further research is required to determine whether any therapeutic modality is more cost-effective than topical salicylic acid.

Conclusion

The viral wart is a common viral infection in children. It usually resolves spontaneously, but treatment is often sought to reduce cutaneous dissemination, and to remove painful or disfiguring warts. In the author's experience, a combination of therapeutic modalities is often required to treat viral warts effectively and quickly. For younger children, relatively painless treatments like topical keratolytics and imiquimod are good options. For older children and adolescents, cryotherapy, surgery, or the combined cantharidin, podophyllotoxin, and salicylic acid lotion are effective options.

Tinea Versicolor

Introduction

Tinea versicolor, also called pityriasis versicolor, is a common benign superficial fungal infection localized to the stratum corneum. It is caused by dimorphic lipophilic fungus in the genus *Malassezia*, a component of the normal skin flora.

As *Malassezia* is a component of the normal flora, tinea versicolor is not regarded as a contagious disease. Predisposing factors include genetic predisposition, warm humid environments, immunosuppression, and malnutrition.

The predominant Malassezia species causing tinea versicolor varies in different populations, and most epidemiological studies were carried out in adults. In temperate climates, *M. globosa* appears to be the predominant species found in the lesions of tinea versicolor [51]. In a Japanese population, *M. restricta* overwhelmingly predominated at ages over 16–18 years in males and 23–29 years in females. *M. globosa* and *M. restricta* together accounted for more than 70 % of Malassezia species recovered [52]. In an Argentinian population, *M. sympodialis* and *M. globosa* were the most commonly isolated species [53].

Epidemiology

- **Tinea versicolor occurs more frequently in tropical areas and most commonly in adolescents and young adults.**
- **The prevalence of tinea versicolor in school children varies greatly in different populations and among different regions within a country.**
- **Family history is often positive for tinea versicolor.**

Tinea versicolor occurs worldwide and more frequently in tropical areas. It occurs most commonly in adolescents and young adults. Occurrence before puberty is uncommon (Fig. 20.6), but can happen, even in the neonatal period [54].

The prevalence of tinea versicolor in school children varies greatly in different populations, from as low as less than 0.24 % in a Taiwanese population [55], to as high as 31 % in an Indian population [56]. Even within a country, the prevalence may vary, e.g., 4.7 % in Ibadan, Nigeria [57] and 22 % in southwest Nigeria [58]; less than 0.24 % in Penghu, Taiwan [55] and 4.4 % in Taitung, Taiwan [59]. In the tropics, there is a sudden resurgence of cases in the hot monsoons [60].

Family history is often positive for tinea versicolor [56]. In a Chinese population, the rate of recurrence was higher in patients with positive family history compared to those with negative family history [61].

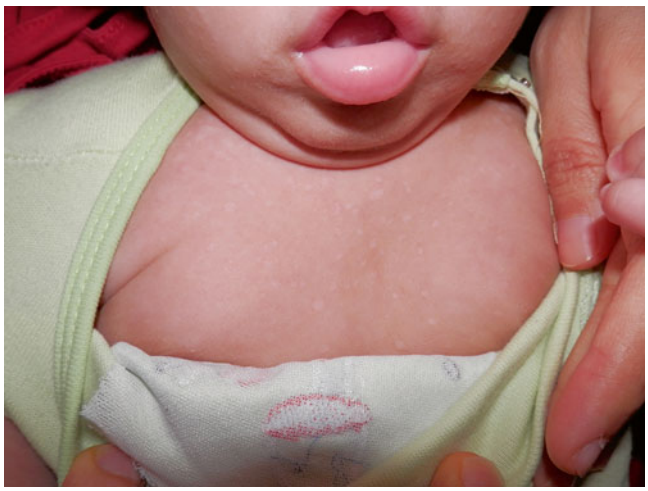

Fig. 20.6 Hypopigmented macules of tinea versicolor in an infant

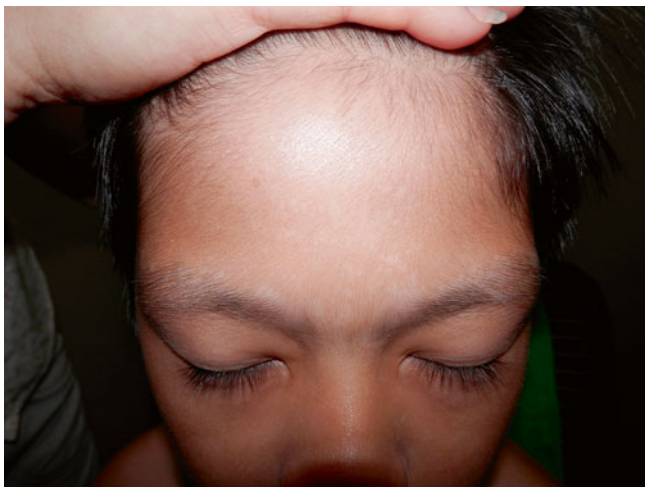

Fig. 20.7 Hypopigmented macules of tinea versicolor on the forehead and eyebrows

Clinical Features

- **Hypopigmented or hyperpigmented macules with fine scales**
- **The face is the commonest site affected in children**
- **Coppery-orange fluorescence is seen under Wood's lamp**

Typical lesions consist of hypopigmented or hyperpigmented macules and patches with fine scales. The color ranges from white to red-brown. Light scratching of the lesions makes the scales more obvious. Lesions commonly occur on the face in children (Fig. 20.7), in contrast to the rarity in adults [56]. The forehead is the usual facial site affected [62, 63]. Other areas usually involved are the neck, trunk, and proximal limbs (Figs. 20.8 and 20.9).

The clinical phenomena of hypopigmentation and fluorescence of the lesions may partly be explained by the generation of tryptophan-derived indole pigments through the action of transaminase 1 (TAM 1) [64].

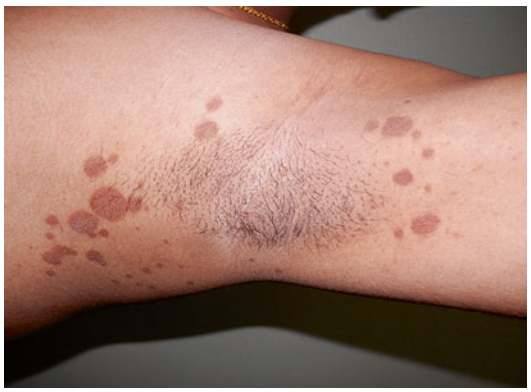

Fig. 20.8 Hyperpigmented macules of tinea versicolor in the axilla

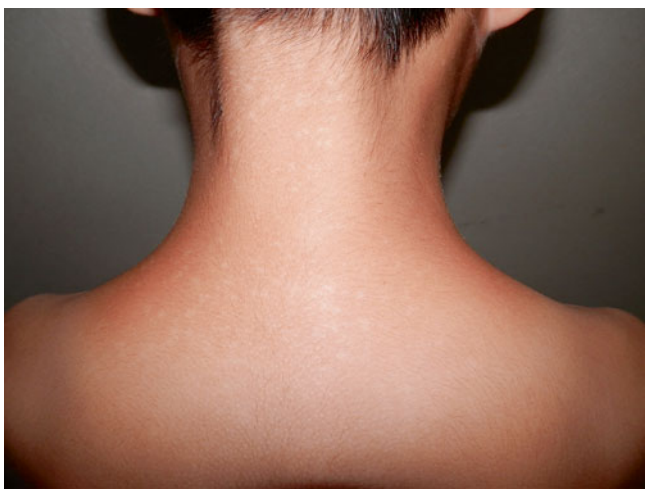

Fig. 20.9 Hypopigmented macules of tinea versicolor on the neck

Management

- **Effective topical agents include selenium sulfide and imidazoles**
- **Prophylactic treatment with selenium sulfide or ketoconazole shampoo once in a week may be necessary to prevent recurrences**
- **Without prophylactic treatment, recurrence is common**

Ultraviolet A (Wood's) light can be used to show the coppery-orange fluorescence of tinea versicolor. The diagnosis can be confirmed by potassium hydroxide examination,

which shows the spores with mycelium ("spaghetti and meatballs") appearance.

Effective topical agents include selenium sulfide and imidazoles, e.g., ketoconazole, clotrimazole, and miconazole. Selenium sulfide or ketoconazole shampoo can be applied to affected areas daily for 2 weeks. Each application can be washed off after 10 min. Alternatively, ketoconazole or miconazole cream can be applied to the affected areas and left overnight for 2 weeks.

Prophylactic treatment with selenium sulfide or ketoconazole shampoo once a week to susceptible areas may be necessary to prevent recurrences. Oral antifungal agents, alone or together with topical agents, can be used for patients with extensive disease. Oral ketoconazole, itraconazole, and fluconazole are effective. In the USA, the FDA has put a major warning on oral ketoconazole due to the risk of liver toxicity. Oral terbinafine and griseofulvin are not effective options for tinea versicolor.

Most topical and systemic treatments used for tinea versicolor are effective compared with placebo. Randomized controlled clinical trials are needed to establish relative efficacy of topical and systemic agents used for treatment and prevention of tinea versicolor [65].

Prognosis

The prognosis is very good. Recurrence is common, but often responds well to treatment. Skin discoloration usually resolves within 3 months.

Ongoing Research

Further research is required to determine why Malassezia, a commensal, causes tinea versicolor in some people but not others.

Conclusion

Tinea versicolor usually occurs in adolescents and adults. It responds well to treatment with topical selenium sulfide or imidazoles, but recurrence is common. The resolution of skin discoloration takes longer than fungal eradication.

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Skin Infections in Immunocompromised Children

21

Maria Teresa García-Romero

Abstract

Infections in immunocompromised children pose a challenge to dermatologists, both because the clinical presentation of common infectious diseases can be greatly modified making diagnosis difficult and because some of these infections have the potential to disseminate and have severe consequences, sometimes fatal. In many cases the skin is the easiest and most accessible way to make a correct diagnosis and initiate adequate treatment. This chapter describes some of the most important bacterial, fungal, viral, mycobacterial, and parasitic infections that children with altered immune systems present.

Keywords

Immunodeficiency • Immunocompromised • Infections • Opportunistic infections

Background/Introduction

Managing patients with alterations in the immune system poses a great challenge to dermatologists, since the clinical presentation and severity of even common infections are greatly modified by the underlying condition.

Epidemiology

- **Common pathogens in immunocompromised patients can be widespread and/or have the potential for serious consequences.**
- **Opportunistic pathogens are more common in immunocompromised hosts.**
- **Depending on the underlying immune alteration, some pathogens will be more common than others.**

Children whose immune system is altered, either temporarily by medications or diseases, or chronically due to genetic or acquired conditions, are susceptible to many diverse types of infections that frequently have dermatologic manifestations. These can be infections caused by common pathogens that frequently affect immunocompetent hosts, but in immunocompromised patients they can be widespread and/or have the potential for serious consequences (e.g., cellulitis or furunculosis). They can also be caused by uncommon pathogens that are opportunistic and are particular of immunocompromised hosts (e.g., aspergillosis, zygomycosis). Finally, skin infections can be primary to the skin or secondary by dissemination from an internal non-cutaneous focus (e.g., fusariosis).

Clinical Presentation

- **Children with primarily cell-mediated immunodeficiency are at risk for invasive infections by fungal (*Candida*, *Cryptococcus*, *Blastomyces*, *Histoplasma*, or *Coccidioides* species), bacteria (*Nocardia*, *Salmonella* species), mycobacteria, and viruses (herpes simplex virus, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus [1].**
- **Patients with myeloproliferative disorders or who have genetic conditions with profound neutropenia are more susceptible to bacterial (*Pseudomonas aeru-***

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***ginosa*, *enterobacteriaceae*, Staphylococcus sp., *Clostridium*) and fungal (Aspergillus sp., Candida sp., *Fusarium* sp., *Mucorales* sp.) infections [1].**

- **Patients with alterations in humoral immunity present with bacteria (*S. pneumonia*, *N. meningitidis*, *H. influenza*), encapsulated gram-negative bacilli, enteroviruses, and parasites like *G. lamblia* [1].**

Depending on the underlying immune alteration, some pathogens are more common than others. Children whose immunodeficiency is primarily cell mediated, such as patients with Wiskott–Aldrich syndrome, Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS), organ transplants, and certain types of cancers are at risk for invasive infections by fungi (*Candida*, *Cryptococcus*, *Blastomyces*, *Histoplasma*, or *Coccidioides* species), bacteria (*Nocardia*, *Salmonella* species), mycobacteria and viruses (herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [1].

Patients with myeloproliferative disorders, who are undergoing chemotherapy or who have genetic conditions which frequently go through periods of profound neutropenia., such as Chediak–Higashi syndrome, Job syndrome, and chronic granulomatous disease, are more susceptible to bacterial (*Pseudomonas aeruginosa*, *enterobacteriaceae*, *Staphylococcus* sp., *Clostridium*) and fungal (*Aspergillus* sp., *Candida* sp., *Fusarium* sp., *Mucorales* sp.) infections [1].

On the other hand, children who have alterations in their humoral immunity due to asplenia, nephrotic syndrome, paraproteinemias, or primary hypogammaglobulinemias present with bacterial (*S. pneumonia*, *N. meningitidis*, *H. influenza*, and encapsulated gram-negative bacilli), enteroviruses, and parasites like *G. lamblia* [1].

Very frequently cutaneous lesions are accompanied by fever and systemic illness, making prompt diagnosis and treatment mandatory.

Pathogenesis

For all infections included in this chapter, there is a common pathogenesis. When the skin barrier is compromised, pathogens can enter and cause localized infection that can then disseminate or become systemic when the host's immune system is not functioning properly. In the same way, infection can disseminate from internal organs such as lungs or gastrointestinal tract to the skin because of the altered immune system that cannot contain it [2].

For didactics in this chapter, we will categorize infections in immunocompromised children by the type of causative agent: bacterial, viral, mycobacterial, fungal, or parasitic. In each category we include epidemiology and demographics, clinical presentation, treatment, prognosis, and ongoing research.

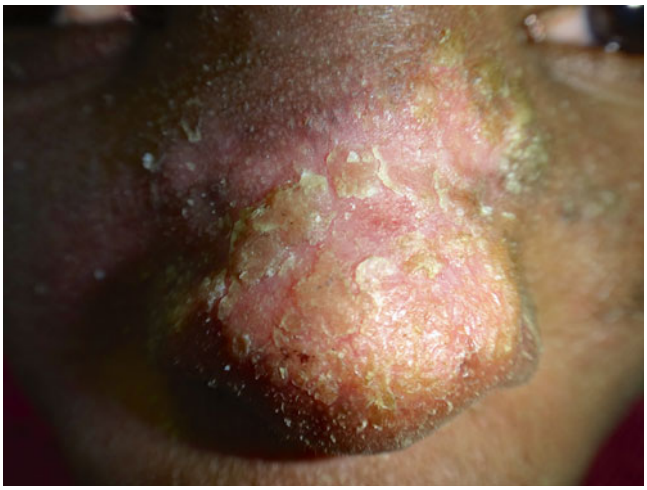

Fig. 21.1 Patient with Job syndrome or Hyper IgE syndrome and extensive impetigo by *S. aureus*

Bacterial Infections

Immunocompromised patients can present infections by common skin pathogens such as *Staphylococcus* sp. and *Streptococcus* sp., but they can be more widespread or severe (Fig. 21.1). There are certain bacteria, however, characteristic of immunocompromised patients that have particular clinical manifestations.

Pseudomonas aeruginosa is a very common cause of bacteremia in neutropenic patients with cancer (5–12 %), particularly acute leukemia. Up to 30 % of the patients with pseudomonal sepsis will have skin lesions [2]. Clinical manifestations include folliculitis, pustules, cellulitis, subcutaneous nodules, and the characteristic ecthyma gangrenosum. This entity presents as erythematous plaques or nodules that progress to become hemorrhagic bullae or necrotic ulcers, is usually associated with fever and general malaise (Fig. 21.2) [3]. Mortality is as high as 27 %, especially when lesions are around the perineal area [4].

Other agents that can cause ecthyma gangrenosum-like lesions are *S. maltophilia*, *Vibrio vulnificus*, *Escherichia coli*, *S. marcescens*, *S. aureus*, *Candida* sp., *Aspergillus* sp., and *Fusarium* sp. [1, 4]. Diagnosis is usually made clinically, and the agent may be identified through tissue culture or blood cultures. Histologically, necrosis and vasculitis with minimal inflammation are characteristic. Treatment includes debridement, cytokine therapy with agents like granulocyte-colony stimulating factor (G-CSF), and intravenous antimicrobial treatment based on susceptibility patterns from culture [2].

Clostridium sp. like *C. perfringens* or *C. septicum* can cause bacteremia in patients with leukemia and malignancies. Skin lesions classically include rapidly spreading cellulitis or spontaneous gangrene. Prompt diagnosis is essential; patients develop sepsis and mortality is as high as 90 %.

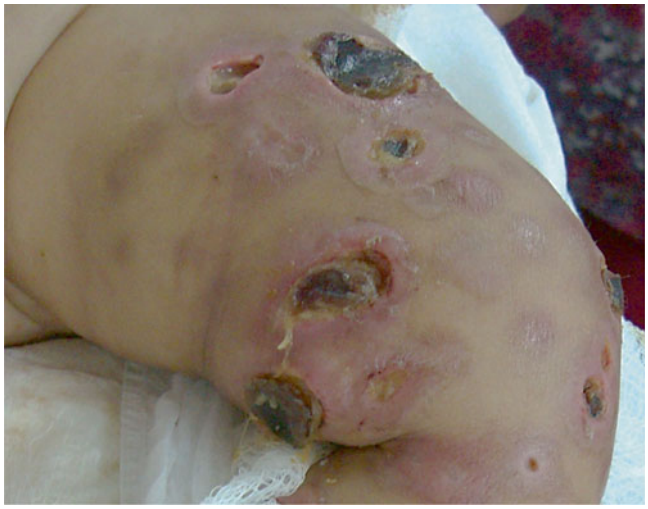

Fig. 21.2 Ecthyma gangrenosum by *P. aeruginosa* in a patient with HIV-AIDS. (Courtesy Prof. R Ruiz-Maldonado)

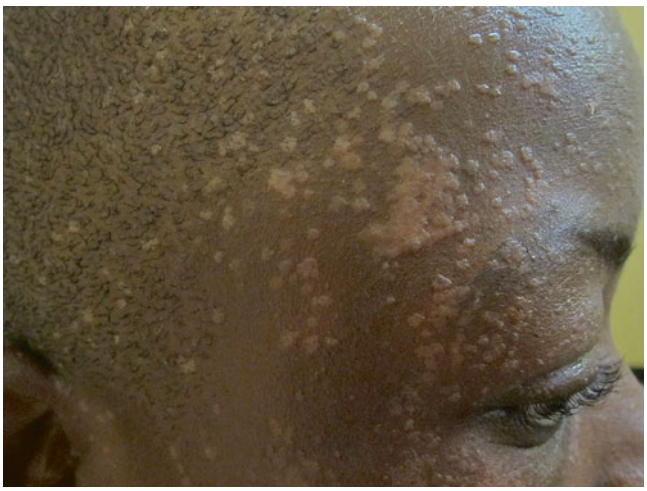

Fig. 21.3 Extensive HPV infection in a patient with HIV-AIDS

Treatment with surgical debridement and antibiotic therapy with penicillin with clindamycin or metronidazole should be initiated promptly.

Nocardia species are gram-positive, acid-fast bacteria that are common causes of infection in hosts with altered immune status. The most common species causing human infection are *N. asteroides*, *N. braziliensis*, and *N. otitidiscaviarum*. Breaks in the skin can result in cellulitis, abscesses, or subcutaneous nodules, often in a sporotrichoid pattern. There can be hematogenous spread to other organs as well. Histologically, branching filaments can be visualized with acid-fast stains, and tissue or blood culture to identify the species should be done. Treatment with sulfonamides combined with another agent according to susceptibility should be initiated and maintained for several weeks after clinical resolution [2].

Viral Infections

HSV infection is common when there is cell-mediated immune dysfunction; both reactivation and primary infection. Immunocompromised hosts present mucocutaneous vesicular or ulcerated lesions that are more chronic, extensive, and severe than in healthy hosts. A Tzanck smear from lesion exudate should be done to identify the typical HSV associated changes, and isolation of the virus in culture is diagnostic. Acyclovir is the mainstay of prevention and therapy; however resistance has increased in the past years [2].

VZV infections are frequent as well, resulting in more widespread and severe presentations of the typical vesiculopustular crusted lesions. These can be necrotic, hemorrhagic, and more painful in immunocompromised patients. Dissemination of the disease to lungs, central nervous system, and liver is also a potential complication to avoid. Treatment with high dose acyclovir should be started promptly. Prophylactic VZV immunoglobulin in these patients is also an option [2].

Cytomegalovirus (CMV) is a common opportunistic pathogen, particularly in post-transplant patients. Infection can be primary through donor organs, blood transfusions, or reactivation. Patients usually present with pneumonitis, hepatitis, encephalitis, retinitis, and bone marrow suppression. Skin lesions are nonspecific. The most common is an erythematous maculopapular eruption that should generate clinical suspicion so the pathogen can be sought for and identified through cultures. Treatment with intravenous ganciclovir is the first-line choice [2, 5].

Human papillomavirus infection (HPV) is a very common infection in all patients, but in patients with cellular immune defects there is persistence of lesions due to decreased clearance of the virus [6].

Epidermodysplasia verruciformis is a rare genodermatosis where there is vulnerability to HPV infection, particularly types 5 and 8. Children with HIV-AIDS infection can have severe HPV infection manifesting as widespread flat warts that are recalcitrant to treatment (Fig. 21.3). It has recently been found that these children have a form of acquired epidermodysplasia verruciformis, which can also be found in children with lymphoproliferative disorders, or organ transplants, where up to 53.8 % have warts that are more chronic and recurrent than in healthy hosts [7–10].

All children who are immunocompromised and have persistent, chronic HPV lesions should have typification of the virus causing the lesions done in order to identify high-risk oncogenic subtypes and treat them more aggressively as well as have strict follow-up.

Treatment options for cases recalcitrant to usual therapy with cryotherapy, salicylic acid, podophyllin, or cantharidin include imiquimod, squaric acid [11], and topical cidofovir [12, 13] with the advantage of decreasing the risk of residual hypo or hyperpigmentation associated to other treatments.

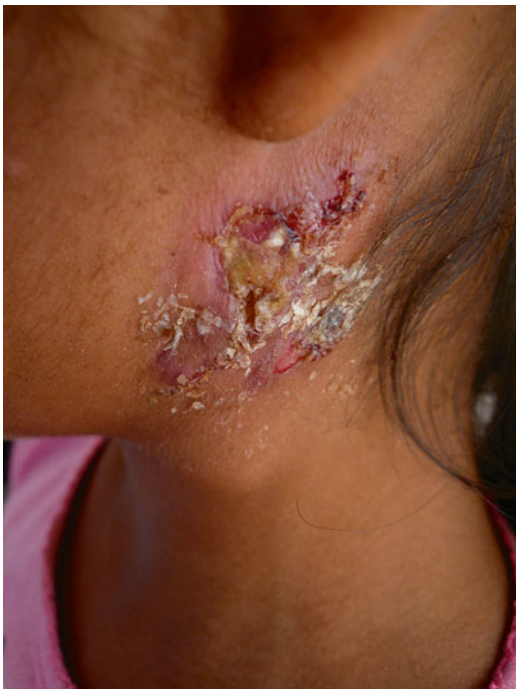

Fig. 21.4 *M. tuberculosis* infection extending from cervical lymph nodes in a severely malnourished girl

Mollusca contagiosa caused by a *poxvirus* is common, and often numerous and severe in immunocompromised children. It can be found in up to 6.9 % of transplanted children; often they are multiple and resistant to treatment [7]. In children with lymphoproliferative diseases atypical lesions can be present, such as giant or ulcerated mollusca [14]. Besides the usual physical or chemical treatments, a new option for treatment of recalcitrant cases in immunocompromised children is topical cidofovir [15, 16].

Mycobacterial Infections

Mycobacterium tuberculosis may produce cutaneous lesions after inoculation from an exogenous source, or dissemination from an endogenous source or hematogenous source. Immunocompromised children with severe malnutrition, malignancies, and HIV-AIDS are most at risk, especially Hispanic and non-Hispanic black children who have higher prevalence of positive tuberculin skin tests and tuberculosis (TB) [17, 18]. Pediatric patients with HIV infection frequently are coinfected with TB (up to 20-fold greater risk) and patients are more likely to be smear negative and nonreactive to skin testing, so a high index of suspicion should be maintained [19, 20]. Skin lesions can vary from purpuric papules to verrucous plaques or abscesses with draining sinuses (Fig. 21.4). Tissue examination for acid-fast bacilli, tissue culture, and histopathology should be done. Treatment with full regimen antituberculous therapy is needed: a 2-month intensive phase of daily isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin followed by a 4-month continuation phase with isoniazid and rifampicin [21, 22].

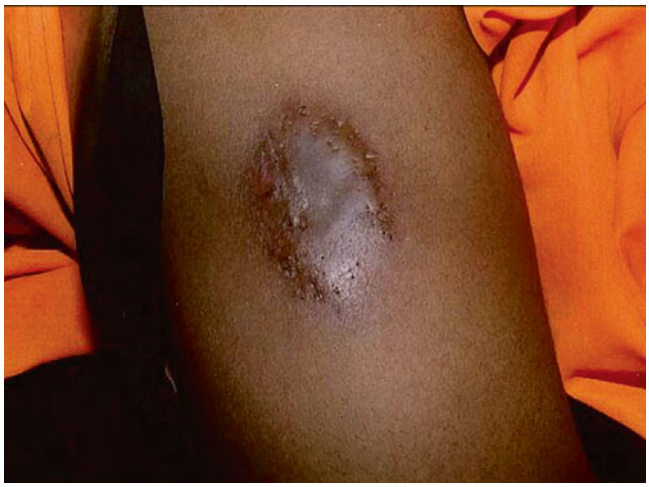

Fig. 21.5 Subcutaneous abscesses caused by *M. chelonae* infection

Systemic bacillus Calmette-Guérin infection (BCGitis) is characterized by multiple and disseminated papulonodular or ulcerated cutaneous lesions associated with systemic involvement after application of BCG vaccine. It presents in patients with severe cellular-inherited immune deficiencies, such as severe combined immunodeficiency or chronic granulomatous disease, and children with HIV-AIDS. The estimated prevalence is between 0.1 and 4.3 per million vaccinated. The treatment includes full antituberculous regimen and interferon-gamma if needed, abscess drainage, and/or local isoniazid injection [17, 23].

Non-tuberculous mycobacteria (NTM) are extremely common causes of infection in immunocompromised children, and very frequently there is no history of skin trauma (contrary to mycobacterial infections in healthy hosts). There are more than 100 species of NTM, and some of the most common pathogens in immunocompromised hosts are *M. fortuitum*, *M. chelonae*, *M. avium-intracellulare*, *M. haemophilum*, and *M. kansasii*. Patients with specific immunodeficiencies, such as interferon-gamma receptor, can present recurrent infections by different species [24]. There is a wide array of cutaneous manifestations associated with these pathogens: papules, vesicles, nodules, ulcers, draining sinuses, and cellulitis-like lesions (Fig. 21.5). Biopsy specimens exhibit granulomatous and suppurative inflammation, and acid-fast bacilli may be observed. The gold standard for diagnosis is tissue culture to identify the causative species and antibiotic susceptibility. Treatment should include at least two antibiotics for at least 3 months [25].

Fungal Infections

Immunocompromised children can present superficial mycosis more frequently than healthy hosts (onychomycosis, tinea corporis, tinea capitis) [26]; usually clinical manifestations are the same but the infection can be more widespread or severe.

Patients with alterations in cell-mediated immunity are most susceptible to fungal infections: those with neutropenia, hematologic conditions, post-organ transplant, and HIV infections. Deep cutaneous fungal infections should always be in the differential diagnosis, since mortality is high if treatment is delayed. Systemic infection should be considered until proven otherwise, as skin lesions can be the first presenting sign. Early biopsies for histopathology, microbial cultures, and direct examination are mandatory for identification of the causal organism.

Candida sp. is the most common pathogen causing disseminated infection in immunocompromised children. The most common isolated species is *C. albicans*, but resistant strains of *C. krusei* and *C. glabrata* are increasing in frequency.

In patients with altered cell-mediated immunity, systemic candidemia is the most frequent presentation with a high mortality if not treated promptly. The second in frequency is disseminated chronic candidiasis (7 %), followed by mucocutaneous candidiasis (particularly in patients with HIV) [27, 28]. Patients with systemic or disseminated candidiasis present persistent fever, various degrees of multiorganic dysfunction, and skin lesions. These are commonly erythematous papules or pustules and often coalesce; crusty, erosive lesions can also be found [29].

Treatment with systemic antifungals should be initiated promptly after blood cultures are taken and susceptibility patterns identified. Catheters and intravascular devices should be cultured and replaced.

Aspergillus sp. are ubiquitous fungi that cause opportunistic infections in immunocompromised patients very frequently, especially in patients with leukemias and lymphomas. Cutaneous aspergillosis can be primary, or secondary through hematogenous spread from a distant focus (up to 11 % of these patients have skin manifestations) or by spread from contiguous tissues (e.g., nasal septum abscesses). Lesions usually arise around catheters, oxygen saturation monitors, IV lines, or sites that were covered with tape or dressings. Clinically, lesions are erythematous plaques or nodules that can develop necrotic eschars or purpuric bullae (Fig. 21.6). Clinical suspicion is crucial, but the definitive diagnosis is histological and mycological through culture of tissue. On histologic exam septate hyphae that branch at acute angles are found [2].

Mortality is high if not treated with amphotericin B or voriconazole for at least 6–12 weeks to avoid recurrence while receiving intensive chemotherapy [29–32].

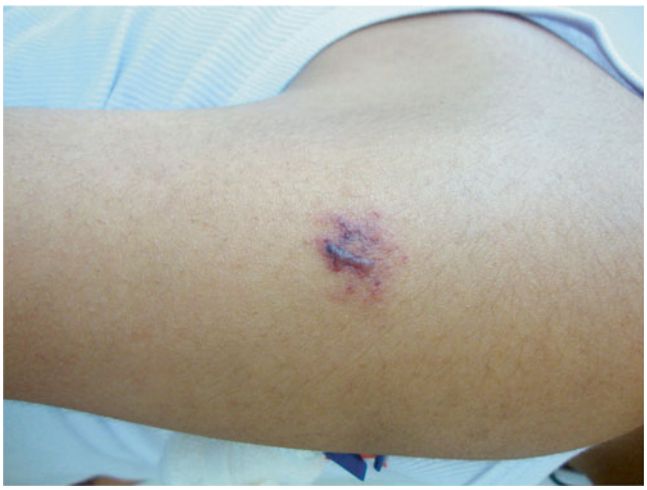

Fig. 21.6 Disseminated cutaneous aspergillosis in a patient with ALL (Courtesy Dr. C Palacios-López)

Fusarium species can cause localized infections in immunocompetent individuals, and disseminated in those severely immunocompromised. They now represent the second most frequent mold causing invasive fungal infection in this population, particularly in neutropenic patients due to hematological malignancies like leukemias and recipients of bone marrow transplants [33, 34], as well as primary immunodeficiencies [34]. The most common species are *F. solani* (accounts for up to 50 % of cases of human infection), *F. oxysporum*, and *F. moniliforme* [34, 35].

Infections by *Fusarium* sp. frequently manifest with skin lesions, which are many times the only source of material to make a diagnosis. In a large case series up to 72 % of the children had skin lesions, and of these, 88 % had disseminated lesions. The most frequent lesions are painful papules and nodules, most of them necrotic (ecthyma-gangrenosum-like) [35], cellulitis, intertrigo, and abscesses. A history of skin breakdown by IV lines or dressings is very uncommon, but some patients develop periungual cellulitis and have pre-existing onychomycosis by *Fusarium* sp. The patients have fever and malaise, which rapidly progresses to fungemia in a matter of days; up to 60 % have positive blood cultures. Invasion of extracutaneous organs via hematogenous spread is likely, and *Fusarium* sp. has been documented to cause infections in almost any organ: lungs, heart, paranasal sinuses, and brain. Histopathologic exam of a skin biopsy shows hyaline, acute-branching septate hyphae among marked inflammation, necrosis, and vascular invasion. These findings can be very similar to those in aspergillosis, so fungal culture and direct examination are crucial.

Mortality is very high, especially in neutropenic patients, unless systemic antifungal therapy is instituted either with or without granulocyte transfusion. Antifungal resistance among species varies so the choice of treatment should be

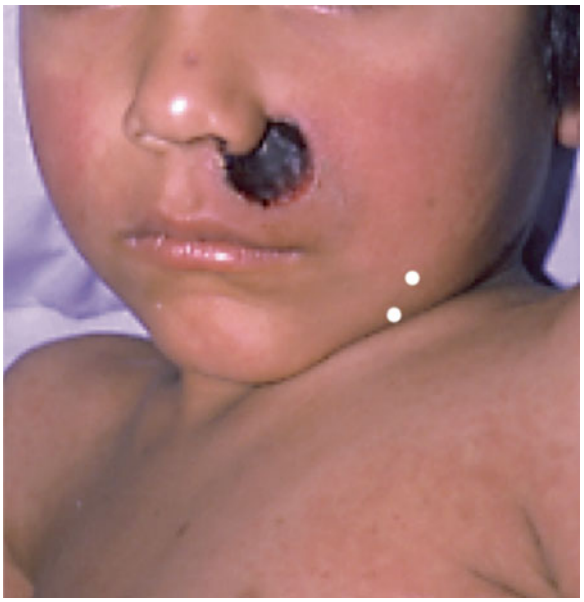

Fig. 21.7 Necrotic ulcer caused by zygomycosis in a patient with AML (Courtesy Prof. R. Ruiz-Maldonado)

directed by results of the fungal culture and susceptibility patterns. Amphotericin B is active against some *Fusarium* species, and the newer antifungal triazole agents such as itraconazole, voriconazole, and posaconazole have also shown good results [33, 34].

Zygomycosis infection is associated with fungi of the *zygomycetes* and the order *Mucorales* (the term mucormycosis should be discouraged because *Mucor* sp. are only rarely the cause of zygomycosis). These fungi are ubiquitous in nature; they can be found in vegetation, bread, and soil. Opportunistic zygomycosis can affect many different organs: rhinocerebral, pulmonary, gastrointestinal, cutaneous, or disseminated. The cutaneous form usually follows inoculation or contact by contaminated material. It is a rapidly progressive infection characterized by tissue destruction and blood vessel invasion. In the past decades, it has been an increasing cause of infection in patients with neutropenia due to hematologic malignancies who are treated prophylactically with voriconazole against aspergillosis. It is also more common in patients with corticosteroid therapy, organ transplantation, and HIV-AIDS [36].

Skin lesions are usually tender erythematous, purpuric nodules, or patches that rapidly progress to necrosis and invade peripheral tissues (Fig. 21.7). Hematogenous dissemination is common, and the mortality rate is very high even after treatment has been started (up to 32 %).

The diagnosis is made histologically from a skin or tissue biopsy. The typical findings are suppurative granulomatous inflammation, necrosis, vascular invasion, and different degrees of thrombosis, and collections of broad non-septated hyphae branched at 90˚ angles. Tissue should be sent for direct examination and fungal culture as well, in order to identify the specific fungus causing the infection and its susceptibility patterns.

Treatment should be started promptly. Ideally it should combine surgical debridement and antifungal treatment with intravenous amphotericin B or posaconazole. The echinocandins and other trizoles such as ravuconazole and voriconazole are inactive against *Mucorales* [37].

Other less common fungal infections in immunocompromised patients are coccidioidomycosis, histoplasmosis, and blastomycosis. They can present with necrotic papules, nodules, or cellulitis. There is usually a history of skin disruption. Treatment with amphotericin B should be started if disease progresses rapidly or in disseminated disease. Other options are voriconazole or caspofungin [29, 38].

Parasitic Infections

Scabies is a common cause of infection in immunocompromised children, particularly those with cell-mediated immune dysfunction. It is a highly contagious condition caused by *Sarcoptes scabiei* var. *hominis*. Patients present with disseminated erythematous crusted papules and vesicles, particularly between the folds and on the scalp. Especially children with HIV-AIDS (up to 2–4 %) can present with Norwegian or crusted scabies, which is characterized by widespread prominent crusted plaques, keratoderma, and fissuring (Fig. 21.8a, b). Many cases have such atypical manifestations that the diagnoses might go unsuspected for many weeks. The definitive diagnosis is made when the scabies mites or their eggs are visualized on microscopical examination of a preparation of skin scrapings, or even by biopsy. These children can fail to respond to the usual treatments like permethrin crème or benzene hexachloride. Treatment with oral ivermectin as a single dose, repeated after 1 week, is an excellent option (Fig. 21.9) [39, 40].

Demodex folliculorum and *Demodex brevis* are ectoparasites that are normal inhabitants of pilosebaceous ducts in healthy persons, and it is controversial whether they cause cutaneous disorders. However, these normally commensal mites can proliferate when there is immune dysfunction and they should be considered in the diagnosis of sudden-onset papulopustular eruptions in immunocompromised patients, particularly patients with lymphoproliferative disorders and HIV-AIDS. Infestation by Demodex sp. can present as pruritic, hyperkeratotic papular eruption on the trunk, upper extremities, and face. The diagnosis can be made by examining skin scraping preparation with KOH under the microscope and by identifying the parasites. Treatment consists of topical permethrin cream, selenium sulfide, benzyl benzoate, and metronidazole. Widespread or severe cases can be treated with oral ivermectin [41–44].

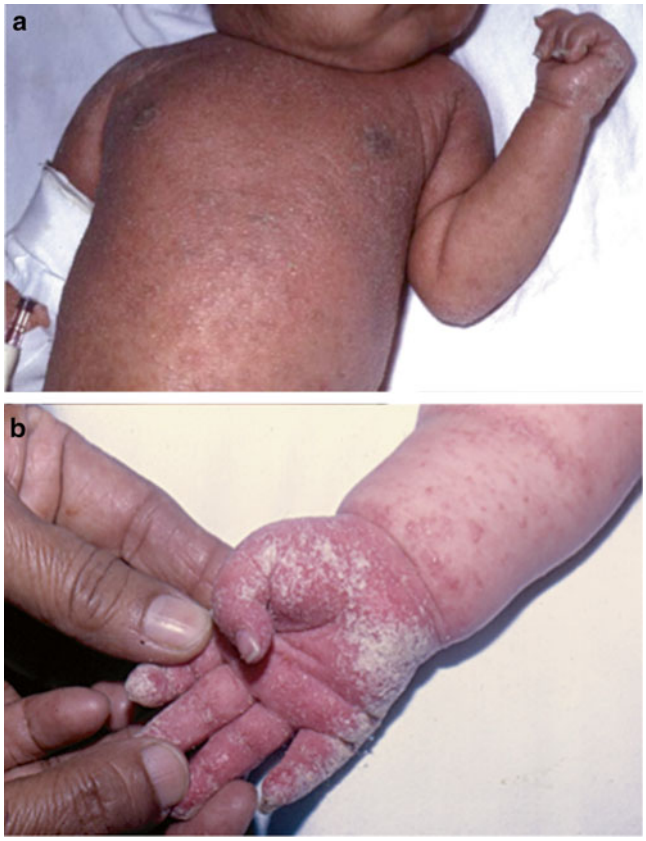

Fig. 21.8 (**a**, **b**) Crusted scabies in a patient with severe combined immunodeficiency (Courtesy Dr. C. Durán-McKinster)

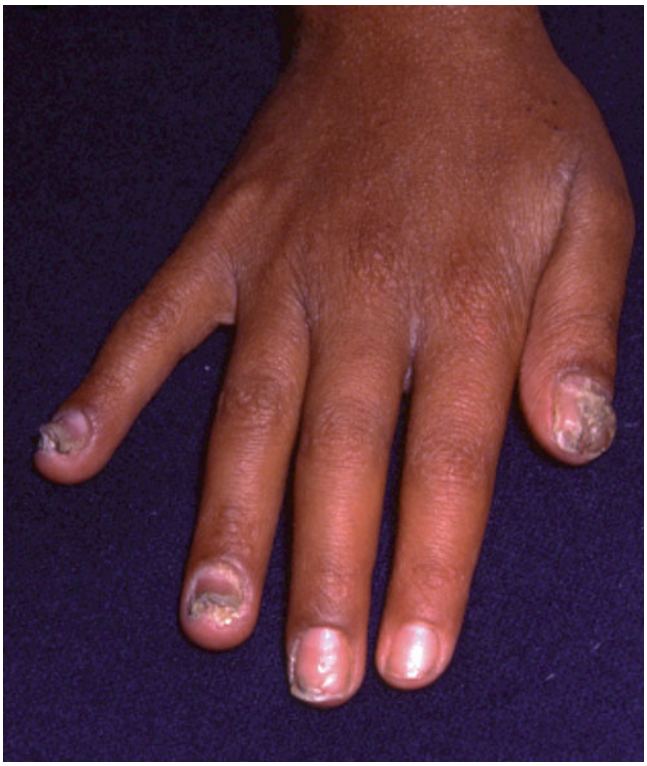

Fig. 21.9 Subungual scabies in a patient with common variable immunodeficiency (Courtesy Prof. R Ruiz-Maldonado)

Prognosis

- The prognosis varies depending on each infection and the host's underlying disorder.
- In general, disseminated deep fungal, bacterial, and mycobacterial infections have a bad prognosis and can be lethal if not treated promptly with the right systemic antibiotic according to resistance patterns.
- The viral and parasitic infections described in this chapter are not lethal, but can cause severe distress and disfigurement to the patients.

Ongoing Research

- Acquired epidermodysplasia verruciformis in the setting of immunosuppression is subject of current research because of the disfigurement and stigma that patients suffer (particularly in HIV-AIDS) and the chronicity of lesions. Some novel treatments being evaluated include glycolic acid, topical cidofovir, imiquimod, and squaric acid [45].
- New antifungals are being evaluated in terms of efficacy against deep fungal infections in the setting of immune dysfunction as well as their side effects, such as ravuconazole, posaconazole, and voriconazole. Particularly this last one has been shown to cause severe idiosyncratic phototoxicity [46].

Conclusions

The diagnosis and management of skin infections in immunosuppressed children are difficult; it requires a high index of suspicion to make a prompt diagnosis and start treatment. In many cases, these infections are recalcitrant and resistant to the treatments used in healthy children, so second-line options need to be used.

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Tropical Infections

22

Héctor Cáceres-Ríos and Felipe Velásquez

Abstract

This chapter reviews some infectious diseases, mainly with cutaneous involvement. These infections are distributed worldwide, especially in the tropical areas. Human bartonellosis, free-living amebiasis, myiasis, and larva migrans are reviewed, emphasizing their cutaneous manifestations.

Human bartonellosis or Carrion's disease is an infectious endemic angiomatosis; although restricted to the Andean mountains in Peru, Ecuador, and Colombia, it may occur worldwide in travelers returning from these endemic areas. Free-living amoebiasis is a severe protozoan disease which has been reported worldwide; it usually involves the central nervous system and sometimes is associated with skin lesions in otherwise healthy children.

Myiasis and larva migrans or gnathostomiasis are diseases caused by larvae accidentally; although distributed worldwide, these diseases occur mainly in poor socioeconomic regions.

Keywords

Human Bartonellosis • Free-living amoebiasis • Myasis • Larva migrans

Human Bartonellosis (Carrion's Disease)

Human Bartonellosis (HB) or Carrion's disease is an infectious endemic angiomatosis produced by *Bartonella bacilliformis*, a gram-negative coccobacillus. The disease is limited to endemic areas of Andean communities in Peru, Colombia, and Ecuador, where lives the principal vector Lutzomyia verrucarum. Human Bartonellosis is characterized by two distinct disease manifestations: an abrupt acute bacteremic illness (Oroya fever) and an indolent cutaneous eruptive angiomatous condition (verruga peruana). Despite being an ancient disease that has affected populations since pre-Inca times, research in this area has been limited and diagnostic and treatment guidelines are based on local evidence reports.

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Introduction

- **Human bartonellosis has two phases: Oroya fever and verruga peruana.**
- **It is an infectious endemic angiomatosis.**
- **The disease is restricted to the Andean mountains in South America.**

Human Bartonellosis (HB) or Carrion's disease is an infectious endemic angiomatosis caused by *Bartonella bacilliformis*, a gram-negative, facultative intracellular, aerobic coccobacillus, member of the alpha-proteobacteria group along with Rickettsia and Brucella. HB has two phases; verruga peruana, the angiomatous and eruptive phase, which follows an acute and febrile phase known as Oroya fever [1]. The eponym Carrion's disease recognizes the contribution of Daniel A. Carrion, a Peruvian medical student who in 1885 asked a fellow student to inoculate him with blood from a warty cutaneous lesion from a diseased patient, in order to test his hypothesis

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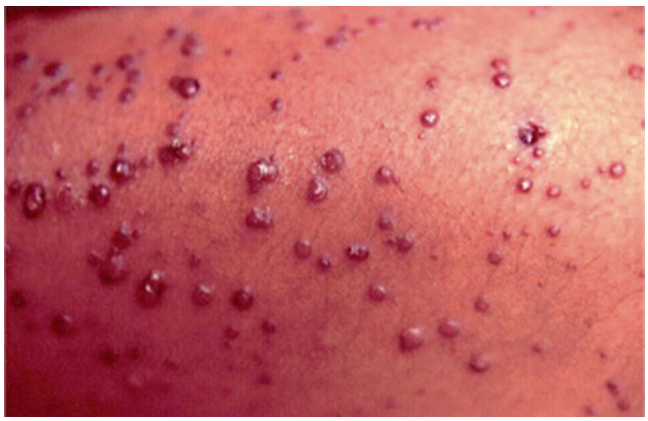

Fig. 22.1 Multiple angiomatous papular lesions of verruga peruana

that the two clinical entities, which were considered at the time to be different illnesses, were actually manifestations of the same disease. His hypothesis was proven to be tragically correct as he developed, and soon after succumbed to, the acute febrile form of the illness hitherto known as Carrion's disease, becoming a martyr of Peruvian medicine [2].

Epidemiology

The disease is restricted to the Andean mountains in Peru [2], Ecuador, and Colombia with unconfirmed reports of cases in Thailand in the 1960s and sporadic cases in Bolivia, Chile, and possibly Guatemala [3, 4]. Classically, endemic areas are confined to inter-Andean valleys positioned at right angle to the prevailing wind and at altitudes between 500 and 3,200 m above sea level [5]. This locality is mainly due to the characteristics of its putative principal vector, Lutzomyia verrucarum, which has a weak, hopping flight and is intolerant of extreme temperatures [2]. The vector has a crepuscular feeding habit and households are heterogeneously affected (18 %).

Clinical Manifestations

- **HB is an acute bacteremic phase named Oroya fever.**
- **The cutaneous phase is an angiomatous eruption called verruga peruana.**
- **Sometimes may be fatal.**

The organism causes two distinct clinical phases. The initial acute phase known as Oroya fever is characterized by malaise, fever, and severe hemolytic anemia. It has a mortality of 44–88 % in untreated individuals during this period [6]. The subsequent phase, known as verruga Peruana, may occur weeks to months after the acute illness, and it is characterized by the eruption of crops of miliary, numular, or nodular skin angiomatous lesions [7] (Fig. 22.1).

Complications are not uncommon in the acute phase and include super-infections, most commonly with salmonella species but also with toxoplasma, histoplasma, and others [8]. Hematological, gastrointestinal, cardiovascular, and neurological complications also occur during pregnancy and infection can lead to miscarriage, premature labor, and maternal death. Young children are the most affected in endemic communities, partly because of predominantly younger population but also due to the presumed protective immunity that develops with repeated infections [2].

Differential Diagnosis

The cutaneous lesions of verruga peruana have a wide differential that includes pyogenic granuloma, hemangioma, bacillary angiomatosis, Kaposi's sarcoma, fibrosarcoma, leprosy (cystoid form), malignant lymphoma, reticuloendotheliosis, yaws, lymphomatoid papillomatosis, angiolymphoid hyperplasia with eosinophilia, varicella, molluscum contagiosum, Spitz nevus, and sarcoma [9].

Treatment

Only studies looking at quinolones and chloramphenicol were found in the literature but none comparing the two. Rifampicin is now the most widely used antibiotic in the chronic phase and most patients respond well: 80 % and 93.1 % respectively in two studies one of which has level 3a evidence [10].

Ongoing Research

Development of effective surveillance tools to increase understanding of the epidemiology of disease, harmonized case and outcome definitions, readiness for outbreak investigation including evaluation of vector control strategies, contact investigations, and environmental and reservoir host studies will all be important [2]. Understanding of immunity and strain diversity is vestigial and advances might yield important insights into pathophysiology.

Free-Living Amoebiasis

Introduction

- **Free-living amoebiasis is a severe protozoan disease.**
- **Caused by free-living amoebas.**
- **Usually causes neurological disease, and sometimes cutaneous disease.**

Free-living amoebiasis (FLA) is a protozoan disease caused by free-living amoebae belonging to genera *Naegleria*, *Acanthamoeba*, and *Balamuthia*, which usually produces severe central nervous system (CNS) involvement, and sometimes is associated with cutaneous disease.

Initially cases of cerebral FLA were ascribed to genus *Acanthamoeba*, but later were thought to be produced by order *Leptomyxida* [11]. However, now the organism is reclassified into the genus *Balamuthia*, to honor William Balamuth. *Balamuthia mandrillaris* denotes the origin of the species isolated from a pregnant baboon that died at the San Diego Zoo [12].

At present FLA is considered an emerging disease causing skin lesions as well as CNS involvement with a fatal outcome if untreated. The infection is more commonly described in inmunocompetent individuals, mostly males, and children. Commonly patients debut with neurological symptoms, whereas in our country, Peru, the skin lesion precedes other manifestations [13].

Epidemiology

Cases of FLA have been reported worldwide, mostly in the American continent, but also in Asia, Australia, and Europe [14]. In South America many cases occur in Mexico, Venezuela, Argentina, Brasil, Chile, and specially in Peru At present, more than 200 cases of primary amoebic meningoencephalitis (PAM) produced by *N. fowleri* have been reported; around 100 cases of granulomatous amoebic encephalitis (GAE) are related to *Acanthamoeba*; and approximately 66 human *Balamuthia* cases have been recognized worldwide [13].

Amoebae are usually found in freshwater lakes, thermal discharge of power plants, hot springs, ponds, streams with still water, sewage, and even in the nasal cavity of healthy persons. Immersion in swimming pools, freshwater lakes, or ponds and any form of immunodeficiency are predisposing factors for *Acanthamoeba* species [15]. There are no identified predisposing factors for Balamuthia infections.

Although the disease may occur at any age, most reported cases are in children and adolescents, especially those produced by *B. mandrillaris* [16].

In Peru a number of cases, 55, have been identified since 1975, all of them with a confirmed diagnosis of amoebic infection of the skin and CNS. Half of the cases occurred in pediatric patients 15 years old or younger; and at least 22 were confirmed cases of *Balamuthia mandrillaris* infection [17].

Clinical Features

- **Skin lesion may precede other manifestations.**
- **Centrofacial plaque with granulomatous appearance and elevated and serpiginous borders.**

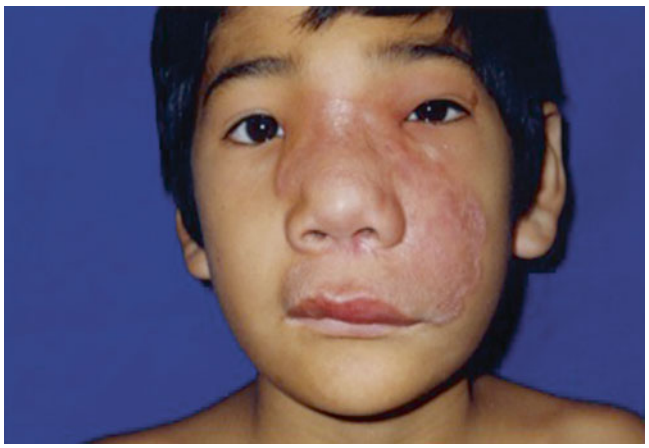

Fig. 22.2 This picture shows centrofacial plaque with a granulomatous appearance and the typical elevated and serpiginous borders

- **Neurological involvement has fatal course.**

FLA produces mainly CNS disease, but may also involve other organs such as eyes, nasal mucosa, and especially skin. In countries like Peru, skin lesion precedes other symptoms. This primary cutaneous lesion can be present for weeks or even months. However, the appearance of neurological disease predicts a poor prognosis [18]. Certainly, the diagnosis is very difficult and its prognosis is very ominous if the patient debuts with CNS involvement; on the other hand, if the patient debuts with skin lesions, there is the possibility of an earlier diagnosis and treatment; therefore it is very important to recognize the cutaneous manifestation of the disease.

Cutaneous FLA

Skin lesions in otherwise healthy children are the most common presentation in Peruvian cases, but in general the disease starts with CNS symptoms. The primary cutaneous lesion occurs in the nasal pyramid and rarely in other areas of the skin. The centrofacial plaque has a granulomatous appearance with typical elevated and serpiginous borders that slowly spread peripherally (Fig. 22.2); ulceration seems to be the exception rather than the rule at least in our cases. Other locations are seen, most frequently the knees, the elbows, and the chest. Many patients present a single lesion but satellite lesions near the larger lesion are not uncommon. Some patients may develop simultaneous lesions on the face and extremities. A few cases have oral involvement, especially of the hard palate. Central facial lesions in untreated patients may progress to a more diffuse infiltration and tumor stage, and CNS symptoms may develop months later, with progressive deterioration and death.

Neurological FLA

The neurological symptoms are classically those of an encephalitis, including headache, fever, and photophobia. As the disease progresses, and some times quite rapidly, other signs, such as seizures, lethargy, and anisocoria, related to increased intracranial pressure, become evident. The patient may present

focal sensorial and motor deficits. The level of consciousness deteriorates, going from lethargy to coma and death.

N. fowleri produces an acute and fulminating primary amoebic meningoencephalitis (PAM), which is characterized by an abrupt onset and fulminant course, that usually affects children and young adults. Patients with PAM present signs and symptoms of meningeal irritation and encephalitis; sudden onset of headache, fever, nausea, vomiting, and stiff neck may progress rapidly to lethargy, confusion, coma, and death in 48–72 h [19].

Acanthamoeba or *Balamuthia* species in debilitated or immunosuppressed patients, produce the so-called granulomatous amoebic encephalitis (GAE), which is a chronic and fatal disease characterized by neurological signs depending on multifocal hemorrhagic and necrotic areas of the brain [20]. Symptoms resemble those of single or multiple space-occupying lesions; hemiparesis, drowsiness, personality changes, and seizures appear early; insidious headache, low-grade fever, stiff neck, nausea, vomiting, and lethargy may be present. Death occurs from 1 week to several months after the onset.

Disseminated FLA occurs especially in the immunosuppressed. Granulomas and amoebae have been found in the adrenal glands, kidneys, liver, lungs, pancreas, spleen, thyroid gland, and uterus [21].

Diagnosis

Direct examination of cerebrospinal fluid in PAM and GAE using a phase-contrast microscope discloses pear-shaped biflagellated motile amoebae. Smears stained with Giemsa, Wright, or hematoxylin and eosin (H&E) disclose the morphology of the amoebae.

N. fowleri and *Acanthamoeba* species can be cultured easily in agar seeded with bacteria like *E. coli* at 37 °C. Cultures of *B. mandrillaris* require monkey kidney cells but are often unsuccessful; a new axenic (cell-free) medium may be more suitable [22].

The skin biopsy may serve as the first clue for the diagnosis of FLA; histopathology of the skin lesions discloses a granulomatous reaction, with multinucleated giant cells, and a mixed inflammatory infiltrate. The amoebae can be seen using routine H&E stains [17].

Differential diagnosis of cutaneous FLA includes mucocutaneous leishmaniasis, rhinosporidiosis, rhinoescleroma, conidiobolomycosis, Wegener's granulomatosis, sarcoidosis, Melkersson Rosenthal syndrome, mid-line granuloma, and cutaneous T-cell lymphoma.

Pathogenesis

The organisms enter the nasal cavity by inhalation of dust, through contaminated water, or in air that contains trophozoites or cysts. After the parasite enters through nasal mucosa, initially involving the olfactory neuroepithelium, it subsequently reaches the CNS by active phagocytosis of sustentacular cells. Due to the contiguity with subarachnoid membranes, amoebae may easily disseminate to other areas of the CNS, producing an acute and fulminating PAM [19].

Therapeutics and Prognosis

Successful treatment of *Naegleria* encephalitis with intravenous and intrathecal amphotericin B has been reported [23]. There is no known effective therapy for *Balamuthia* infection. Miconazole, 5-fluorocytosine, pentamidine, sulfadiazine, fluconazole, itraconazole, amphotericin b, azithromycin, and clarithromycin have been used with variable results.

A report of successful treatment of two cases with CNS involvement included flucytosine, pentamidine, fluconazole, sulfadiazine, and a macrolide; phenothiazines were also added in one case [24]. Both patients received long-term therapy for more than 5 years.

Long-term albendazole 20 mg/kg/day and itraconazole 10 mg/kg/day have been used as therapeutic alternatives in some of our patients with promising results.

Ongoing Researches

In the past years, advances have been made regarding knowledge about the ubiquity of the amoeba in the environment, its worldwide distribution especially in South America, the patients at risk particularly those of Hispanic origin, the diagnostic methods including those based on molecular biology, and the different therapeutic strategies that have resulted in survival of patients. A recent report dealing with solid organ transplant transmission of this infection has made it a subject of interest in transplant medicine [25].

Conclusion

As more and more cases are reported , this entity should be called to the attention of dermatologists, infectious disease specialists, neurologists, pediatricians, and internists. Cases do occur all over the world, and many diagnoses will be missed, unless we have a high index of suspicion . It is very likely that this condition may explain some of the cases previously described as lethal mid-line granuloma.

Table 22.1 Modified from Fabio Francesconi and Omar Lupi [4]

Ecological classification	Description
Specific/obligatory	Parasite dependent on host for part of its life cycle
Semispecific/facultative	
Primary	Free living and may initiate myiasis
Secondary	Free living and unable to initiate myiasis; may be involved once animal is infested by other species
Tertiary	Free living and unable to initiate myiasis; may be involved when host is near death
Accidental/pseudomyiasis	Free-living larva and not able to complete its life cycle; causes pathological reaction when accidentally in contact with the host

Myiasis

Introduction

- Myiasis is an infestation with maggots.
- Occurs in poor socioeconomic regions and forests.
- Treatment consists of many local remedies.

It is an infestation of live human and vertebrate animals with dipterous (two-winged) larvae (maggots) which, at least for a certain period, feed on the host's dead or living tissue, liquid body substance, or ingested food [26]. The distribution of human myiasis is worldwide, with more species and greater abundance in poor socioeconomic regions of tropical and subtropical countries [27].

The anatomical classification system is based on the one proposed by Bishopp and later modified by James and by Zumpt [28] (Table 22.1).

- Sanguinivorous or bloodsucking
- Cutaneous myiasis, furuncular and migratory
- Wound myiasis
- Cavitary myiasis, where the infestation receives the name of the affected organ, e.g., cerebral myiasis, aural myiasis, nasal myiasis, and ophthalmo-myiasis.

Epidemiology

Myiasis is worldwide, the most common flies that cause the human infestation are *Dermatobia hominis* (human botfly) (Fig. 22.3) and *Cordylobia anthropophaga* (tumbu fly).

Dermatobia hominis is the most important cuterebra fly and the most common cause of myiasis in the Americas. American warble fly, tropical both fly, colmoyote, moyocuil (both in Mexico, meaning "mosquito worm"), suglacuru (from "between breasts" in French Guyana), and berne (in Brazil).

The real importance of human myiasis is unknown, and identification of the species responsible for a case of myiasis is rarely done. Epidemiological data on human myiasis are scant, and registration of the cases is not usually obligatory. Healthcare professionals judge myiasis to be a disease of minor importance, the larva and dressings are normally discarded without further examination. In some countries, domestic and empirical treatments of the patients are made by family members, reducing the number of the cases seen in medical facilities.

Fig. 22.3 Dipteran larva obtained from a furuncle-like nodule. The patient is from the south of Mexico. Courtesy Dr. Natalia Deveaux. Med Vet

Clinical Presentation

- Cutaneous myiasis occurs due to poor hygiene.
- Furuncular myiasis is the most common form.
- Cavitary form could be fatal.

Myiasis is considered, in most cases, an embarrassing and repugnant disease to patients and to healthcare professionals. Poor hygiene and low socioeconomic status are the most important risk factors for acquiring myiasis [30]. Another important factor is an abundance of exposed preexisting suppurative lesions that attract and stimulate the deposit of eggs by the female insect.

Cutaneous myiasis, together with wound myiasis, is the most frequently encountered clinical form [31]. Furuncular myiasis (warble) occurs after the penetration of the dipteran larva into healthy skin where an erythematous, furuncle-like nodule develops, with one or more maggots within it. *Dermatobia hominis* and *Cordylobia anthropophaga* are the most common causative agents of furuncular myiasis.

The typical furuncular lesion is a papule or nodule with a central punctum that exudes serosanguineous or purulent fluid. In the central pore, the presence of the parasite may be evidenced by the direct visualization of the posterior part of the larva. The number of larvae within the lesion varies with the species. Pruritus, pain, and movement sensation are the most reported symptoms, and they usually happen suddenly at night, preceding the fluid leak [29]. Although a furuncle-like lesion is the most common presentation of furuncular myiasis, clinical variants have been described, such as vesic-

ular, bullous, pustular, erosive, ecchymotic, and ulcerative lesions. The lesion almost always heals completely, without leaving any trace. Clinical variants and severe cicatricial outcomes are more commonly seen in malnourished children. The most commonly reported complication of furuncular lesions is secondary bacterial infection [29].

Treatment

Treatment consists of many local remedies for removing the larva such as application of glue, pork fat, mineral oils, and petroleum jelly to suffocate the maggot, but the results can often be less than optimal.

Oral treatment of human myiasis is based on anecdotal reports, and most of the experience comes from veterinary medicine [32].

Ivermectin, a semisynthetic agent of the macrolide family (derived from a natural substance, avermectin, which is obtained from actinomycetes) is the most common agent used for the treatment of myiasis. Introduced for medical use in the 1980s as a broad-spectrum antiparasitic drug, ivermectin proved to be effective against most intestinal parasites, most arthropods, and some nematodes. Medical use in humans started as a prophylactic treatment of filariasis caused by *Onchocerca volvulus*, *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. Lately, it has also been used for the treatment of scabies, with excellent results. Different therapeutic regimens have been adopted for ivermectin use in the treatment of myiasis: just one oral dose of 150–200 μg/kg of body weight is the most commonly prescribed dose [33, 34].

Prognosis

Myiasis is generally self-limiting and in many cases not dangerous to the host. However, complications can arise. With increasing global travel, trade, and immigration it is likely that general practitioners and also physicians will encounter more cases of myiasis in the future. Travelers should be aware of the condition so that effective preventive measures could be taken to avoid infestation [26, 29].

Ongoing Research

Recently, a few centers systematically use larvae for debridement of chronic non-healing wounds and have coined the term "biosurgery" for this approach. The future will show whether debridement with larvae becomes a safe and cost effective treatment for patients with necrotizing wounds or chronic ulcers.

Conclusion

Myiasis in humans can produce furuncular, creeping, or traumatic lesions. Each fly has a specific geographical region ranging from the woodlands of North America to the tropical regions of South America and Africa. Length, shape, color, life cycle, number of offspring, and arrangement of spines are all physical characteristics that differentiate the many different species of larvae and thus are useful in determining and predicting the severity of infestation.

Larva Migrans, Gnathostomiasis

Introduction

- **Gnathostomiasis is a zoonosis caused by larvae.**
- **Usually results from eating undercooked fish (ceviche). It may cause cutaneous and visceral lesions.**

Gnathostomiasis is a zoonosis caused by the third-stage larvae of the genus *Gnathostoma*. Human beings are an accidental and abnormal host for *Gnathostoma* resulting from eating raw or undercooked intermediate hosts (e.g., fish, eels, and loaches) or paratenic hosts (e.g., crustaceans, freshwater fish, and mammals) containing the third-stage (L3) larvae. The larvae cannot mature in humans and keep migrating in the skin, subcutaneous tissues, or other organs [35, 36].

Epidemiology

The endemic foci of gnathostomiasis have been predominantly distributed in Japan and Southeast Asia, particularly Thailand, but the disease is also endemic in other countries. Human cases have also been reported in India, Australia, Brazil, and parts of South Africa, and it has been regarded as an emerging disease [37].

In more recent years, it has become an increasing problem in Central and South America, particularly in Mexico, Guatemala, Peru, and Ecuador due to the consumption of ceviche, which is raw-fish marinated in lime [37, 38].

Changes in dietary habits are the main cause of expansion of the geographical range of the disease. From the reports, it seems that the important factor is where the sushi is eaten rather than simply the consumption itself, suggesting that cases tend to occur as a result of consumption of food from local restaurants in countries where the disease is endemic and where few regulations if any govern the sourcing or storage of fish for consumption. They suggest that such restaurants tend to use cheaper local freshwater or brackish-water fish, in contrast to sushi bars and restaurants in the West, which primarily use more expensive saltwater fish which are

free of *Gnathostoma* spp. and harbor relatively few potentially transmissible parasites [39].

The genus *Gnathostoma* belongs to the order spirurida and family *Gnathostomadiae*. Of all the species, the four medically important species are *G. spinigerum* (most common and important), *G. hispidum*, *G. doloresi*, and *G. nipponicum*. Speciation can be made under microscope by observation of the distribution and shape of the cuticular spines over the body.

Gnathostoma is an etiological agent of both cutaneous larva migrans (CLM) and visceral larva migrans (VLM). However, in contrast to the CLM caused by hookworm, it is usually deeper and may involve muscles and appear as an intermittent migratory swelling. Visceral gnathostomiasis is more dangerous and it may affect any organ—eyes, CNS, lungs, and the gastrointestinal tract. Laryngeal involvement may lead to dyspnea and stridor. CNS involvement causes eosinophilic myeloencephalitis and may lead to severe complications.

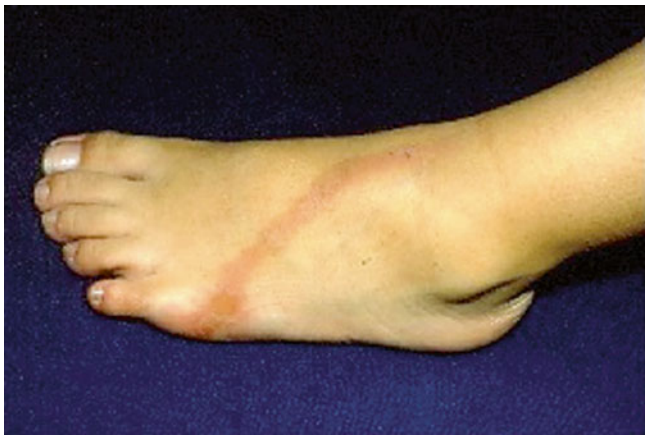

Fig. 22.4 Gnathostomiasis. Courtesy Prof. Ruiz-Maldonado

Clinical Presentation

- **Malaise and fever when larva migrates.**
- **Migratory swelling of subcutaneous tissue.**
- **The worm may penetrate inner tissues.**

The triad of migratory lesions, eosinophilia, and obvious exposure risk is highly suggestive of the diagnosis of gnathostomiasis. The clinical features can be divided into immediate symptoms, a cutaneous form, and a visceral form. Within 24–48 h of ingestion of *Gnathostoma* organisms, patients may develop nonspecific signs and symptoms such as malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain. These symptoms occur as the larva migrates through the stomach or intestinal wall and the liver and may last for 2–3 weeks [40]. A marked generalized eosinophilia usually develops in association with larval penetration of the gastrointestinal wall, with reported levels of >50 % of the total white-cell count. The larval worm then migrates to the skin through the subcutaneous tissue causing the typical migratory swellings (Fig. 22.4) and from here may penetrate into deeper tissues and viscera to involve the lungs, eyes, ears, gastrointestinal and genitourinary systems, and rarely, but often fatally, the CNS (visceral disease). The majority of infections result only in cutaneous disease, within 3–4 weeks after ingestion of the larvae, but the onset of symptoms may be delayed for months and even years [41, 42]. As the chronic stage begins and the larva enters the subcutaneous tissues, the eosinophilia and systemic features usually subside.

The definite diagnosis is established by isolation of larvae from the lesions, but this is often difficult in migratory skin lesions. The detection rate of larvae in skin biopsy specimens was only 24–34 % of the cases.

Of interest, the majority of the cases reported herein involved consumption of marinated fish (ceviche) in Lima, Peru, where arguably all fish used for such recipes is saltwater fish. This would be in contrast to most cases reported in the literature, which have implicated almost exclusively freshwater fish [37].

Treatment

For many years there was no effective treatment for gnathostomiasis, and surgical excision of the larvae remained the only effective management. Various drugs were tried both in animal models and in humans without success, including thiabendazole, praziquantel, metronidazole, diethylcarbamazine, and quinine.

Albendazole is a broad-spectrum antihelminthic which has proven efficacy against intestinal helminths and also extraintestinal helminthic infections such as opisthorchiasis, hydatid disease, and cutaneous larva migrans.

Ivermectin has also been investigated for use in the treatment of gnathostomiasis, and it seems that its efficacy is similar to that reported for albendazole.

Initial treatment is not always successful, and second courses of treatment have been needed in some cases. Either albendazole or ivermectin may be used in sequence in such patients, and both have been used with successful outcomes for initial treatment failures [38].

Prognosis

In travelers returning from endemic areas, initial relapse occurred up to 7 months after the treatment, and the maximum period between two relapses is 15 months [43].

A pragmatic approach would be that if the patient was asymptomatic after 12 months of treatment, this would be sufficient evidence of cure, particularly if supported by a resolution of any eosinophilia and a decrease in ELISA levels. In the event of relapse, a new 12-month follow-up period should be commenced.

Ongoing Research

Future trials would be useful to investigate the use of combined treatment with both albendazole and ivermectin and to determine whether relapse rates are lower with combination drugs than with monotherapy.

The definitive diagnosis of gnathostomiasis can be made by recovering the migrating larvae from skin lesions, but this procedure can be difficult because of the migratory behavior of this particular parasite. However, it can be clinically diagnosed by obtaining a history of eating raw or partially cooked fish, intermittent subcutaneous or cutaneous migratory swelling, and eosinophilia [44]. Immunologic approaches have been developed to diagnose gnathostomiasis, including a cutaneous test, agglutination, immunofluorescence, enzyme-linked immunoabsorbent assay, and Western blotting. Some of these tests use excretion–secretion products to detect antibodies in patients because specific functions attributed to the excretion–secretion products of nematodes are invasion, and migration through host tissues, facilitation of feeding, and evasion of host immune responses. However, for the development of these tests, previous characterization of the humoral immune response against the *Gnathostoma* spp. was necessary.

The IgG subclasses have been shown to provide improved specificity over the total IgG antibody array for the diagnosis of many parasitic infections, such as ascariasis, echinococcosis, leishmaniasis, filariasis, and gnathostomiasis caused by species of *Gnathostoma* other than *G. binucleatum* [45].

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Part V

Neonatal Skin Diseases

Histiocytosis

23

Blanca Del Pozzo-Magaña and Irene Lara-Corrales

Abstract

Histiocytosis or histiocytic disorders comprise a large and diverse group of entities that have as common denominator infiltration and/or abnormal accumulation of histiocytes within blood and other tissues. In many of these disorders, the skin plays a key role in diagnosis, and may be the only organ involved. In skin of color, histiocytic disorders can present with different characteristics and look different than in lighter skin tones. The purpose of this chapter is to review some of the histiocytic disorders that affect mainly the pediatric population and highlight differences that might be present in the different skin tones of children of color.

Keywords

Histiocytosis • Langerhans cells • Non-Langerhans cells • Juvenile xanthogranuloma • Benign cephalic histiocytosis • Hemophagocytic lymphohistiocytosis

Abbreviations

BCH	Benign cephalic histiocytosis
CSHRH	Congenital self-healing reticulohistiocytosis
GEH	Generalized eruptive histiocytoma
HLH	Hemophagocytic lymphohistiocytosis
ICH	Indeterminate-cell histiocytosis
JXG	Juvenile xanthogranuloma
LC	Langerhans cells
LCH	Langerhans cell histiocytosis
MPS	Mononuclear phagocytic system
MRH	Multicentric reticulohistiocytosis
MS	Multisystem
PNH	Progressive nodular histiocytosis
RDD	Rosai–Dorfman disease
SHML	Sinus histiocytosis with massive lymphadenopathy
SS	Single-system
XD	Xanthoma disseminatum

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Introduction

There is a very wide spectrum of skin manifestations reported in histiocytic disorders. Nearly all racial and ethnic groups are affected; however, some conditions are extremely rare making it difficult to identify patterns of presentation in different skin tones. To our knowledge, there is no specific cutaneous manifestation of histiocytosis associated with darker skin tones, but a few specific features can be observed. In patients with Fitzpatrick types III–VI that are more richly pigmented, melanocytes have a more labile response to irritation and inflammation resulting in an higher risk of postinflammatory hyperpigmentation or hypermelanosis [1]. The location of melanin in the skin determines the color pigmentation; it tends to be darker (browner) if the excess melanin is in the epidermis, in contrast when melanin is in the dermis the color may vary from gray to blue [2]. It is also known that

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Table 23.1 Contemporary classification of histiocytic disorders

Disorders of varied biological behavior	Malignant disorders
Dendritic cell related • Langerhans cell histiocytosis • Secondary dendritic cell processes • Juvenile xanthogranuloma and related disorders • Solitary histiocytomas of various dendritic cell phenotypes **Macrophage-related** 1. Hemophagocytic syndromes • Primary hemophagocytic lymphohistiocytosis: Hemophagocytic syndromes(familial and sporadic) • Secondary hemophagocytic syndromes: Infection-associated Malignancy-associated Other 2. Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) 3. Solitary histiocytoma with macrophage phenotype	**Monocyte-related** 1. Leukemias (FAB and revised FAB classifications) • Monocytic leukemia M5A and B • Acute myelomonocytic leukemia M4 • Chronic myelomonocytic leukemia 2. Extramedullary monocytic tumor or sarcoma **Dendritic cell-related** • Histiocytic sarcoma (localized or disseminated) Specify phenotype, follicular dendritic cell, interdigitating dendritic cell, etc. **Macrophage-related** • Histiocytic sarcoma (localized or disseminated)

Adapted from Favara et al. Med Pediatr Oncol. 1997;29 (3):157–66

the increment of pigment in the skin may complicate the identification of erythema or yellowish pigmentation [3]. On the other hand, when inflammation is severe enough it can destroy the melanocytes and lead to hypopigmentation. Both hyper- and hypopigmentation may be seen occasionally in the same patient [2].

The Histiocyte

The term histiocyte is used to identify cells of monocyte/macrophage and Langerhans cell/dendritic cell lineages, also known as mononuclear phagocytic system (MPS) [4]. Previous studies suggested that histiocytes evolved from different cell precursors such as monocytes, lymphocytes, or mesenchymal cells [5]. More recently it has been proven that histiocytes originate from CD34+ hematopoietic stem cells in the bone marrow [6]. Cells under the influence of TNFα and GM-CSF follow two different pathways: CD14-negative or CD14-positive pathways. The CD14− cells evolve into Langerhans cells (LC), while CD14 + cells become interstitial/dermal dendrocytes or monocytes/macrophages [5].

Histiocytes play a key role in mediating local immune response by presenting antigens to B and T lymphocytes [7]. Monocytes and macrophages are "professional phagocytes" that fight against microorganisms and clear the body of undesirable particles [4, 5]. MPS cells in comparison to lymphocytes are very versatile and capable of evolving into different phenotypes depending on the tissue in where they are found [8].. Clinical manifestations of histiocytic disorders are greatly diverse and have a wide spectrum of severity, ranging from benign skin lesions to multisystemic and fatal disorders [9].

Current classification [10] divides histiocytic disorders in two major groups: a) those of varying biologic behavior and b) malignant classification. Each of these categories is further divided into dendritic cell or monocyte/macrophage cell lineage [5] (see Table 23.1).

Dendritic Cell Lineage

Langerhans cell histiocytosis (LCH), previously known as Histiocytosis X, is a condition characterized by a clonal proliferation of CD1a+ LC. LCH is the type of histiocytosis observed with higher frequency [5, 11]. Clinical presentation and prognosis vary depending on the site and number of organs affected. Organs most often involved are bones, skin, lymph nodes, and parenchymal organs (liver, spleen, lungs, and bone marrow) [12–15]. Children with LCH may present with single-system (SS) or multisystem (MS) disease and have diverse outcomes: it may resolve spontaneously, respond well to the therapy, become a chronic recidivating condition, or have a rapidly fatal result [12].

Epidemiology

- LCH is rare in children.
- LCH affects 5–6 million children per year between the ages of 1 and 15.
- Incidence in children <1 year is around 15 million per year.

LCH is considered a rare disease. In children under the age of 15 it has been estimated to affect 2.2–8.9 per million every year [13, 16]. Since 30–50 % of cases present in patients older than 15 years, the actual incidence for pediatric age is likely higher, probably around 11–12 per million/year [5]. Incidence rates range from 1.3 per million per year in children age <1 year to 2.0 per million per year in the 10–14-year age group [17]. Several studies suggest that there is a slightly higher prevalence in males 2.2–1.1/1 [18, 19]. In general, median age of diagnosis has been reported

between 1 and 4 years of age [13, 14]. There is no ethnic association; however it has been reported to be very rare in blacks [19].

Etiology

The precise etiology of LCH is unknown [20]. The immune mechanisms underlying LCH are still not fully understood, although important progress has been recently made. Controversy remains whether LCH is a reactive or a neoplastic disorder. Some of the studies that support the latter have demonstrated that LCs from non-pulmonary lesions are monoclonal based on a pattern of highly skewed X-chromosome inactivation [21]. There is also evidence of cell-cycle deregulation within lesions, and the presence of telomere shortening of LCH cells [22]. Its association with lymphoma and acute lymphoblastic leukemia also upholds this theory [21]. Studies in twins and familial presentation have also suggested a possible genetic predisposition [22]. Another theory states that LCH is a reactive disease due to an immature deregulation between LCs and T lymphocytes. Viruses including human herpes virus type 6, cytomegalovirus, and Epstein–Barr virus have been implicated as triggers for this process; however, there is not enough evidence to support the hypothesis that LCH results from a viral trigger [22]. Smoking has also been associated with LCH in adults. It has been shown that cigarette smoke increases the number of LCs in the bronchial epithelium and might be one of the precipitants for pulmonary LCH [20]. More recently, Badalian-Very et al. demonstrated that 35/61 cases of LCH (57 %) exhibit somatic activating mutations in the proto-oncogene *BRAF-V600E1* [23]. This has been previously observed in premalignant cutaneous nevi, melanoma, papillary thyroid cancer, colorectal and lung cancer, low-grade ovarian carcinoma, and pediatric low-grade glioma [21]. On the basis of LCH cell clonality and the presence of activating somatic BRAF mutations in most patient samples, some authors consider that LCH needs to be considered as a neoplastic disease [24].

Classification

Historically, different variants of LCH were described: eosinophilic granuloma, Letterer–Siwe disease, Hand–Schüller–Christian syndrome, Hashimoto–Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, LC granulomatosis, type II Histiocytosis, and non-lipid reticuloendotheliosis. Later, all these were grouped under the name of Histiocytosis X by Lichtenstein in 1953 [25].

Currently, LCH is more commonly classified according to organ system involvement and then subdivided into single or multisite involvement [13]. The Histiocyte Society's treatment protocol for LCH categorizes patients as those with single-system disease (involving a single site), those with single-system disease affecting multiple sites (multifocal), and those with multisystem disease [10].

Clinical Presentation

- Clinical manifestations vary widely depending on organs/systems affected.
- LCH is classified into single-system disease or multisystemic disease.
- Most common organ affected is the bone.
- Skin is the second most commonly affected organ.
- Skin manifestations are polymorphous: red papules, vesicles, hemorrhagic, scaly, and seborrheic-like eruptions have been described.
- Scalp and folds are more commonly affected.

Single-System Disease

Isolated organ involvement is termed single-system disease (SS-LCH). The skeletal system is the most commonly involved location in LCHs. Lesions may manifest as painless, isolated bone lesions or as multiple lesions accompanied by severe dysfunction and deformities [20]. In children the skull and femur are the most common sites affected [26]. The term *eosinophilic granuloma* was previously used to describe the chronic localized form of LCH affecting bone [8]. Up to 40 % of lesions affecting the skull may associate diabetes insipidus due to pituitary infiltration [26]. Historically, the triad consisting of bone disease, diabetes insipidus, and exophthalmos in a child with chronic, progressive multifocal involvement was called *Hand–Schüller–Christian disease* [8, 19].

The second most commonly affected organ is the skin [15, 16, 18] Skin lesions are typically the first manifestation of LCHs in patients under 1 year of age [27, 28]. LCH can present with a wide range of cutaneous findings (Figs. 23.1, 23.2, 23.3, and 23.4). The three main types include: (1) infiltrating lesions (nodules and/or plaques that may ulcerate), (2) extensive papules and plaques with scale or crusts, and (3) seborrheic dermatitis-like or eczematous-like lesions [29]. Other lesions can be purpuric, and present with necrosis. The spectrum of color found on the cutaneous manifestations goes from hypopigmented, yellowish, red-brown to hyperpigmented lesions and this can vary according to the underlying Fitzpatrick skin type [30] (Table 23.2).

The most common site of skin involvement is the scalp, followed by the trunk and groin; however, several case reports also include perianal, genital, limb, and facial [11, 28, 30–33]. Mucosal and nail disease are characterized by nodules and/or ulcerations, but disruption of tooth eruption, nail dystrophy, paronychia, and hemorrhagic bed nails can also be seen [34].

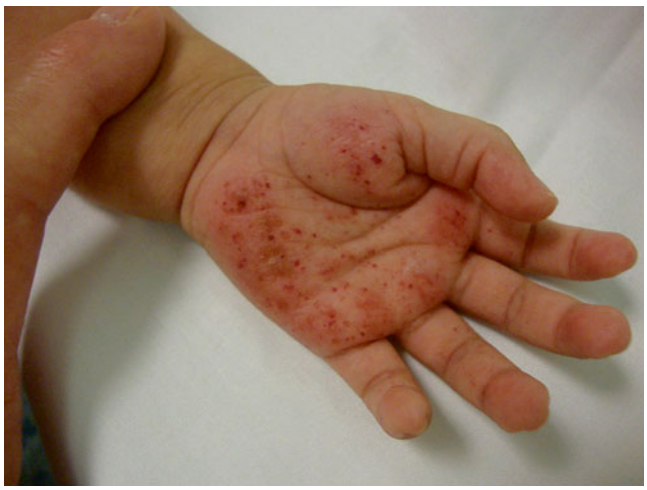

Fig. 23.1 Infiltrated erythematous papules with purpura and crusting on the palm and abdomen in patient with LCH. Courtesy Dr. Duran-McKinster

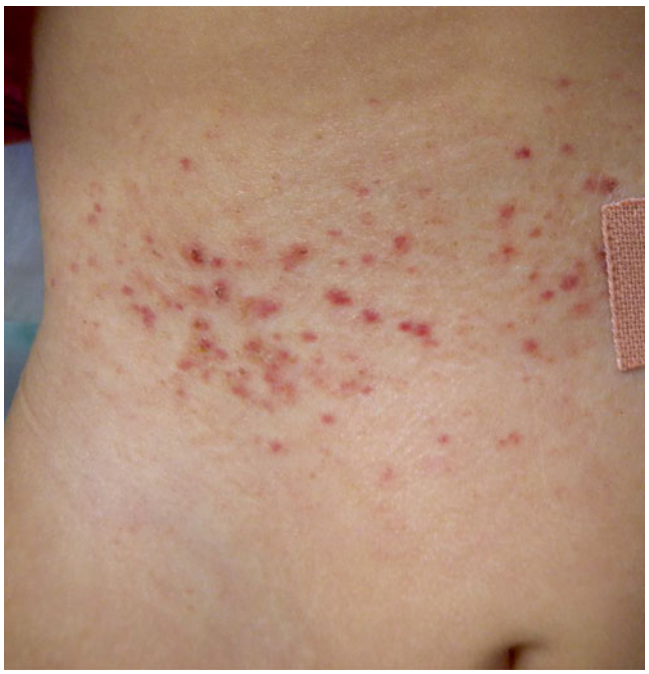

Fig. 23.2 Infiltrated erythematous papules with purpura and crusting on the palm and abdomen in patient with LCH. Courtesy Dr. Duran-McKinster

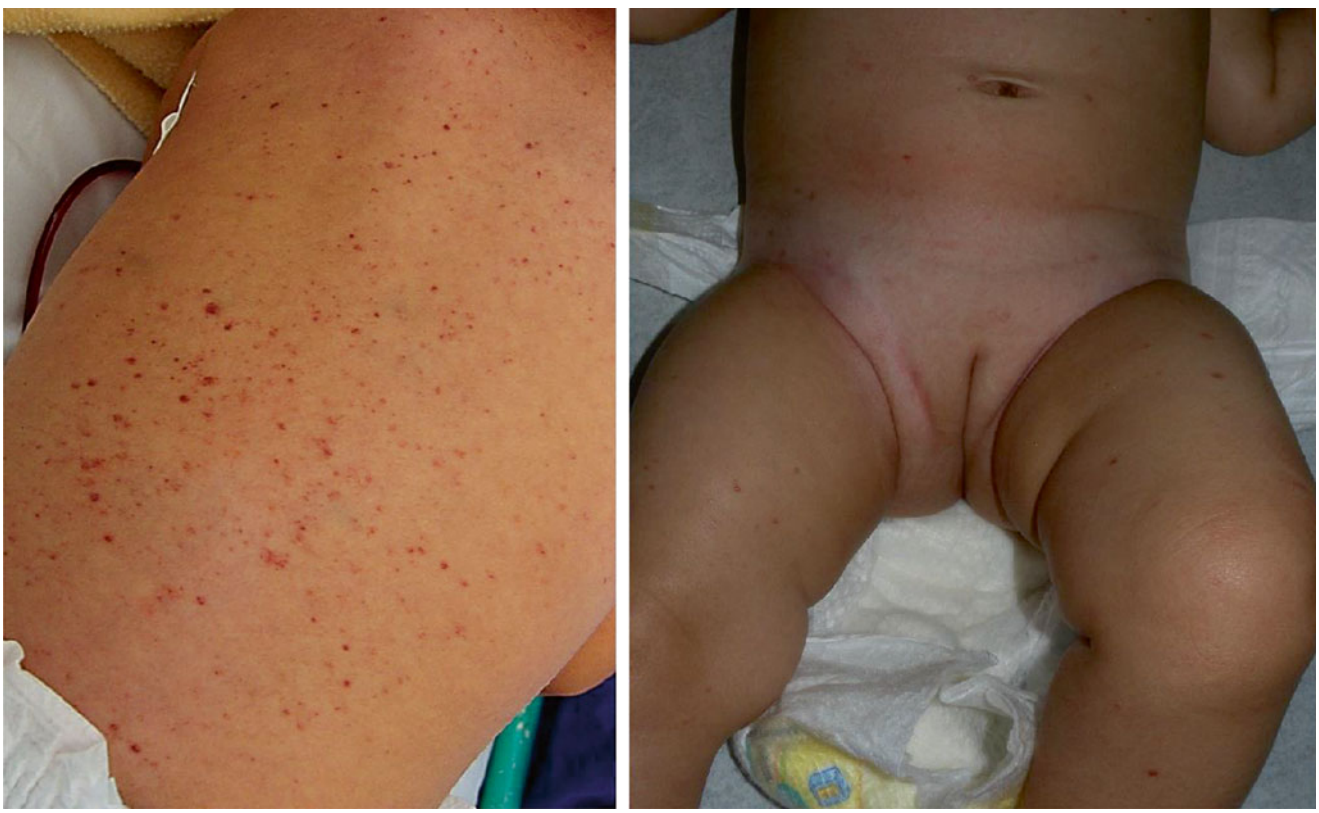

Fig. 23.3 (**a**) Multiple infiltrated erythematous papules with purpura on the back of patient with LCH. Courtesy Dr. Duran-McKinster, (**b**) Scattered erythematous papules on an infant with LCH

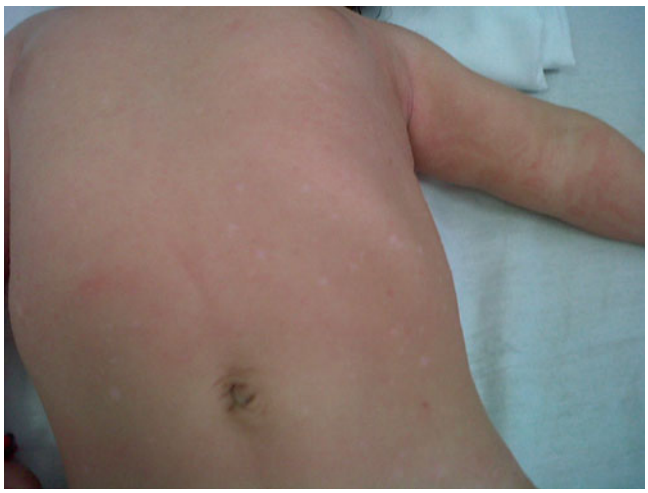

Fig. 23.4 Hypopigmented macules on the abdomen of a child with LCH. Courtesy Dr. Duran-McKinster

Table 23.2 Skin lesions described in children with Langerhans cell histiocytosis

• Infiltrating nodules/plaques (may be ulcerated)
• Flesh-colored to yellow or red-brown papules covered with scales/crust
• Hypopigmented papules
• Papular xanthomas-like
• Seborrheic dermatitis-like lesions (scalp)
• Eczematous dermatitis-like lesions
• Bilateral auricular discharge
• Perianal lesion (vegetative/ulcerated)
• Purpuric/petechiae and necrotic lesions
• Intertriginous lesions (diaper, behind the ears, axillae)
• Molluscum contagiosum-like lesion
• Blueberry Muffin lesion, vesicles/bullae lesions(congenital)
• Darier's disease-like and urticarial lesion (less often described)
• Nodules and mucosal ulcerations (altered dentition)
• Nail changes include dystrophy, paronychia, and bed nail bleeding

Among skin-only LCH, congenital self-healing reticulohistiocytosis (CSHRH) deserves special consideration in children. Previously known as *Hashimoto–Pritzker disease*, this condition usually presents at birth in an otherwise healthy baby and tends to resolve spontaneously during the first months of life. Progression of CSHRH to a multisystem disease has been reported, but some authors consider that this may represent two different entities, since CSHRH and the progressing form of skin-only LCH are indistinguishable clinically and immunohistochemically. Multisystem LCH in the neonatal period has poor prognosis and has been associated with high mortality rates. It has been reported that half of patients initially diagnosed as a skin-only condition actually had multisystem disease [35, 36]. Skin manifestations during the neonatal period do not differ from other age groups: red-brown papules, nodules, seborrheic-like lesions, vesicles, pustules, and hemorrhagic lesions are commonly described, and particular to this age group a "blueberry muffin baby" has also been reported [35].

Multisystemic Disease

Multisystemic disease is diagnosed when two or more systems are affected [18]. MS-LCH is subclassified as low risk or high risk depending if there is or no involvement of lymph nodes, bone marrow, spleen, lungs, or liver [37]. Bone involvement including facial bones, sinuses, maxilla, anterior or middle cranial fossa, with intracranial tumor extension, is also considered high risk [18]. Virtually, almost every organ or organ system can be affected by LCH. Multisystemic disease may or may not be characterized by organ dysfunction [13].

Multisystemic disease, formerly *Letterer–Siwe disease*, is the most aggressive form of LCH. Its frequency in relation to other LCH types varies from 3 to 75 % depending on the series reported [15, 16, 27, 28]. In children, MS disease tends to occurs more frequently before the age of 5 years with a peak incidence between 1 and 4 years [28]. Initial symptoms include anorexia, failure to thrive, and fever. Other manifestations depend on the specific organ affected. The most frequently reported include local pain or swelling (bone involvement), erythematous or weeping eczematoid rash affecting scalp, ear canals, abdomen, and intertriginous areas, including diaper, and otitis media with discharge, cough, tachypnea, hemoptysis, lymphadenopathy, and hepatosplenomegaly [26, 34]. Patients also have laboratory abnormalities like elevated sedimentation rate, thrombocytosis, leukopenia, anemia, and thrombocytopenia [16].

Diagnosis

Once the diagnosis of LCH is suspected, a full work-up (complete blood count with differential, blood chemistries including liver function tests, coagulation studies, urinalysis) and a biopsy from the organ affected or the most accessible lesion should be taken. Histological findings of LCH are distinctive. Lesions are characterized by an accumulation of mononuclear and multinucleated LC mixed with abundant mature eosinophils, as well as some neutrophils and small lymphocytes. LC have grooved, folded, indented, or lobulated vesicular nuclei. They are typically positive for immunohistochemical stains CD1a, langerin (CD207), S-100 protein, and CD68. The distinctive features of LCH are the Birbeck granules, a rod- or tennis-racket-shaped structure seen in electron microscopy; however, the latter is no longer recommended since it has been shown that the expression of Langerin fully correlates with the presence on electron microscopy of Birbeck granules [18, 19]. Additionally,

skeletal radiographs (X-rays), abdominal ultrasound, and MRI are also necessary for diagnosing bone, liver, spleen, or central nervous system involvement.

Treatment

- In SS-LCH disease lesions may resolve spontaneously; thus observation alone is acceptable.
- Local treatment such with curettage and/or topical or intralesional steroids may be indicated in some cases.
- In MS-LCH treatment includes vinblastine and prednisolone.
- In high-risk patients with reactivation, prolonging initial chemotherapy has reduced mortality.

There are different treatment modalities for LCHs depending on the affectation or number of sites involved. Patients with unifocal or single disease may receive no treatment other than observation, since most patients recover spontaneously, or they can be given, in the case of bony lesion, local treatment such as curettage, intralesional steroid injections, or localized radiation. Oral indomethacin is another option for bone lesions due to its action as an analgesic and anti-inflammatory agent. For skin lesions topical steroids are the standard option [20]. Mustard 0.02 % applied topically and PUVA have also been reported to be effective to treat skin lesions of LCHs [22, 26].

Systemic therapy for multifocal or multisystemic disease is guided by hematology/oncology teams and includes chemotherapeutic protocols. Hematopoietic stem cell transplantation is also a current therapeutic option, with a moderate success, for adults and children if high-risk organ involvement is present, or they don't respond to other therapeutic approaches [18, 38].

Prognosis

Patients with SS-LCH have an excellent prognosis, although sequelae have been reported. Bone sequelae develop in 3–42 % of patients [37] and include compression of vertebral bodies, orthopedic deformities, growth plate involvement, destruction of the orbit, tooth loss, and hearing impairment. Diabetes insipidus presents as a result of cranial bone involvement and may be accompanied by growth hormone deficiency [20]. This is most often seen in patients with multisystemic disease (until 40 %). In the skin, the most common cutaneous sequelae is scarring, (up to 30 %) and its extent and severity depend on the side of involvement [37].

The risk of SS-LCH disease progressing to MS-LCH disease is about 10 % [19]. For children with multisystemic disease and on recommended treatment an overall survival rate at 5 years of 94.4 % has been recently reported [22]. Children younger than 2 years at diagnosis have a higher risk of permanent consequences and increased morbidity and mortality due to the likelihood of developing multiorgan dysfunction [13, 27]. However, the mortality in these patients has been reduced to 10–20 % after the introduction of combined schemes of steroids and cytostatics [39, 40]. Disease recurrence in children varies depending on the series but has been reported up to 50 % in multifocal bone disease when patients are treated with single-agent chemotherapy, radiotherapy, or observation only [26].

Ongoing Research

The Histiocytosis Association Research Program's primary objective is to identify and fund initiatives aimed at better understanding the physiopathology of LCH and finding more effective treatments and a potential cure. The following are some of the ongoing studies on LCH:

Analysis of Jagged2 Signaling in Langerhans Cell Histiocytosis
Caroline Hutter MD, PhD
Children's Cancer Research Institute/St. Anna Kinderspital—Vienna, Austria

Research Infrastructure for Clinical and Translational Research in Langerhans Cell Histiocytosis (LCH)
Carlos Rodriguez-Galindo MD
Dana-Farber Cancer Institute—Boston, Massachusetts USA

Whole Exome Sequencing of Langerhans Cell Histiocytosis
Barrett Rollins MD, PhD; Astrid G.S. van Halteren PhD
Dana-Farber Cancer Institute—Boston, Massachusetts USA
Leiden University Medical Center—Leiden, The Netherlands

Histiocyte Society Clinical Trials Database System LCH-IV Treatment Protocol Study
Histiocyte Society Executive Board
LCH Study Reference Center—Vienna, Austria

Juvenile Xanthogranuloma and Related Disorders

Juvenile xanthogranuloma (JXG) and related disorders are a miscellaneous group of dendritic cell disorders that have a common denominator: the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of LCH, which are Birbeck granules, S-100 +, CD1a+ [41]. As proposed by Weitzman and Jaffe in 2005, the JXG family is comprised of different entities that can be divided into (1) cutaneous non-LCH such as benign cephalic histiocytosis, JXG, generalized eruptive histiocytoma (GEH), adult xanthogranuloma, and progressive nodular histiocytosis, (2) cutaneous with major systemic component like xanthoma disseminatum, and (3) systemic non-LCH or Erdheim–Chester disease [42, 43] (Tables 23.3 and 23.4).

Table 23.3 Juvenile xanthogranuloma and related disorders

	Epidemiology	Clinical presentation	Treatment
BCH	Infancy <1 year	Multiple lesions Yellow to brown papules Face and neck	Self-resolving (8–48 months)
JXG	Most common of non-LCH Infancy and childhood	Solitary to multiple lesions Yellow-brown papules or nodules Systemic involvement Variants: giant, mixed or plaque-like, clustered Face, neck, trunk	Self-resolving (1–6 years) Surgical removal
GEH	Adults	Red-brown to red-blue or pale erythematous papules and/or nodules Trunk and proximal limbs	Self-resolving
PNH	Young adults in their 3rd–4th decades	Several to hundred yellowish-brown papule/nodules Trunk, head, neck	Non self-resolving, surgical treatment
XD	3rd decade of life Males	Hundred of red-brown to yellow discrete papules and nodules Face and trunk and affects flexures and folds Mucosal involvement progressive forms with systemic involvement	Seldom self-resolving (5–28 years) Surgical excision, electrocoagulation, cryotherapy, radiation, antimetabolites, anticancer drugs
ECD	Usually adults	Long bones, skin, retro-orbital tissues Systemic involvement Multiple yellow to red-brown papules/plaques Symmetric distribution	Corticosteroids, radiotherapy, chemotherapy, and immunotherapy
ICH	No age predilection	Red to brown multiple papules/nodules distributed mainly over the trunk and extremities	Surgical removal, chemotherapy, 5 % fluorouracil, thalidomide, pravastatin, narrowband UVB

BCH Benign cephalic histiocytosis, *JXG* juvenile xanthogranuloma, *GEH* generalized eruptive histiocytoma, *PNH* progressive nodular histiocytosis, *XD* xanthoma disseminatum, *ECD* Erdheim–Chester disease, *ICH* indeterminate-cell histiocytosis

Table 23.4 Macrophage-related disorders

	Epidemiology	Clinical presentation	Treatment
HLH	Infancy and childhood	Genetic and acquired Fever (severe and persistent), bicytopenias, (platelets <100 × 109/L, neutrophils <109/L), hepatitis and splenomegaly Skin: purpuric, macular, papular, erythrodermic, or morbilliform eruptions	Combinations of immunosuppressive therapy and pro-apoptotic chemotherapy
SHML	Children and young adults	Painless bilateral, massive cervical lymphadenopathy Skin: xanthoma-like, yellowish or reddish-brown papules/nodules Respiratory and digestive system involvement	Corticosteroids, chemotherapy, low-dose interferon, and radiation therapy
MRH	Adults	Involvement of skin, joints (arthritis), and mucosa Solitary or multiple coalescing tender papule/nodular lesions Face, scalp, hands mainly dorsum, lateral fingers, and periungual	Nonsteroidal anti-inflammatory drugs (NSAIDs) corticosteroids, etanercept, methotrexate, and cyclophosphamide

HLH hemophagocytic lymphohistiocytosis, *SHML* sinus histiocytosis with massive lymphadenopathy, *MRH* multicentric reticulohistiocytosis

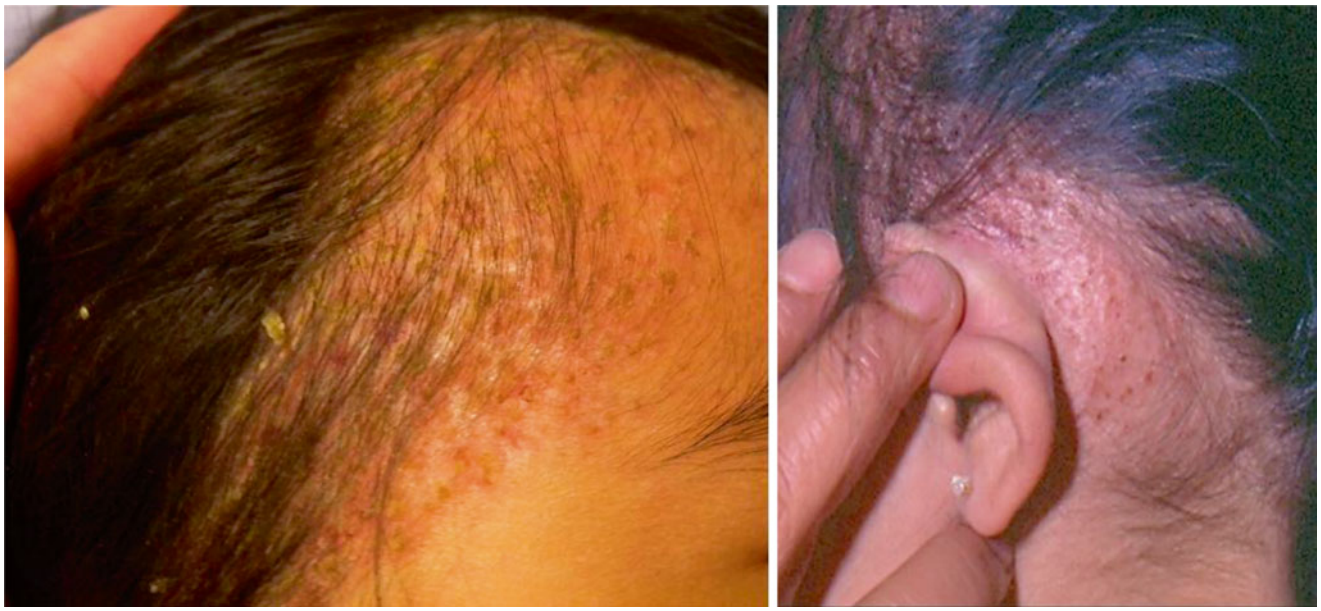

Fig. 23.5 (**a**) Seborrheic dermatitis-like lesions in patient with BCH. (**b**) Retroauricular infiltrated papules in patient with BCH (courtesy Dr. Duran-McKinster)

The JXG family has a broad clinical spectrum, ranging from solitary or multiple skin lesions to large deeply situated masses to widespread disease with systemic involvement. Histological appearance of all subtypes is very similar and often indistinguishable from one another. They present positivity to factor XIIIa, CD68, CD163, l fascin, CD 14, and are negative for CD1a and S-100 proteins [42, 44].

Epidemiology

Disorders belonging to the JXG family are considered uncommon, and their specific frequency is unknown. These disorders have been reported in children and adults of all races. JXG is considered by far the most common type of non-LCH [8].

Cutaneous Non-LCH

Benign cephalic histiocytosis (BCH) (Figures 23.5, 23.6, 23.7, and 23.8) is an uncommon presentation of non-LCH. After been described by Gianotti et al. in 1971, more than 50 cases in various races have been reported [45]. The literature does not provide any data on the frequency or geographic variation of BCH. BCH usually presents during the

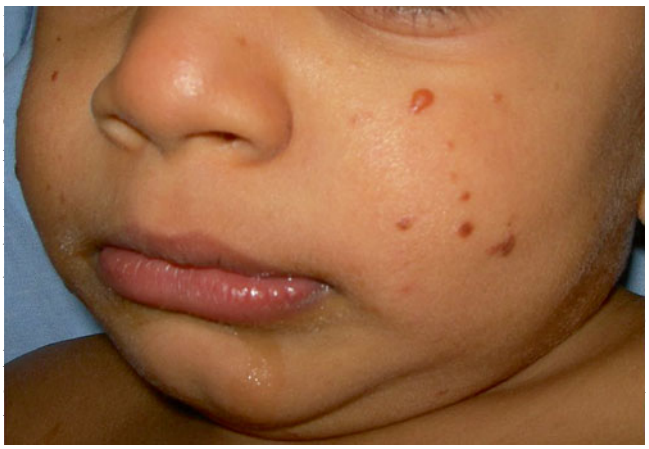

Fig. 23.6 *Dark brown* papules in an infant with BCH

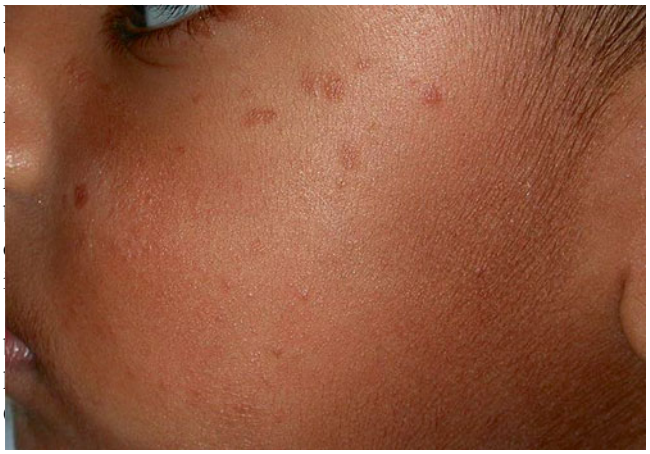

Fig. 23.7 Residual mild atrophy and hyperpigmentation in a child with BCH

nuclei and lymphocytes [51]. Typically, the BCH immunohistochemistry lacks expression of CD1a and S-100 protein; however some late reports have shown some focal or weak S-100 positivity [50].

Although the precise etiology of the BCH remains unknown, several authors agree that together with JXG and GEH, these disorders belong to a wide spectrum of non-LCH, sharing some clinical and histological features [45, 48, 54]. Moreover, transformation of BCH lesions into JXG has also been reported [55]. Differential diagnosis of BCH includes LCH, warts, urticaria pigmentosa, lichenoid sarcoidosis, and multiple Spitz nevi [47, 51]. Since spontaneous remission is observed in all cases, no treatment is recommended [54].

Juvenile Xanthogranuloma

JXG is the most common type of non-LCH. Most cases occur in infancy and childhood, but adults may be affected [56]. Although it has been reported worldwide, its absolute frequency is unknown. In 2005, Janssen and Harms reported a case series of 129 cases of JXG in pediatric patients and found a relative incidence of 0.52 % (Kiel Pediatric Tumor Registry) which was lower than that reported for LCH (3.25 %) within the same period (ratio of JXG to LCH of 1:6.2) [57].

JXG was initially described by Adamson in 1905 and named congenital xanthoma multiplex [58]. Mc Donagh in 1912 used the term nevoxanthoendothelioma considering that the lesions were derived from endothelial cells [41]. Later, in 1954, Helwig and Macknay outlined its histopathologic

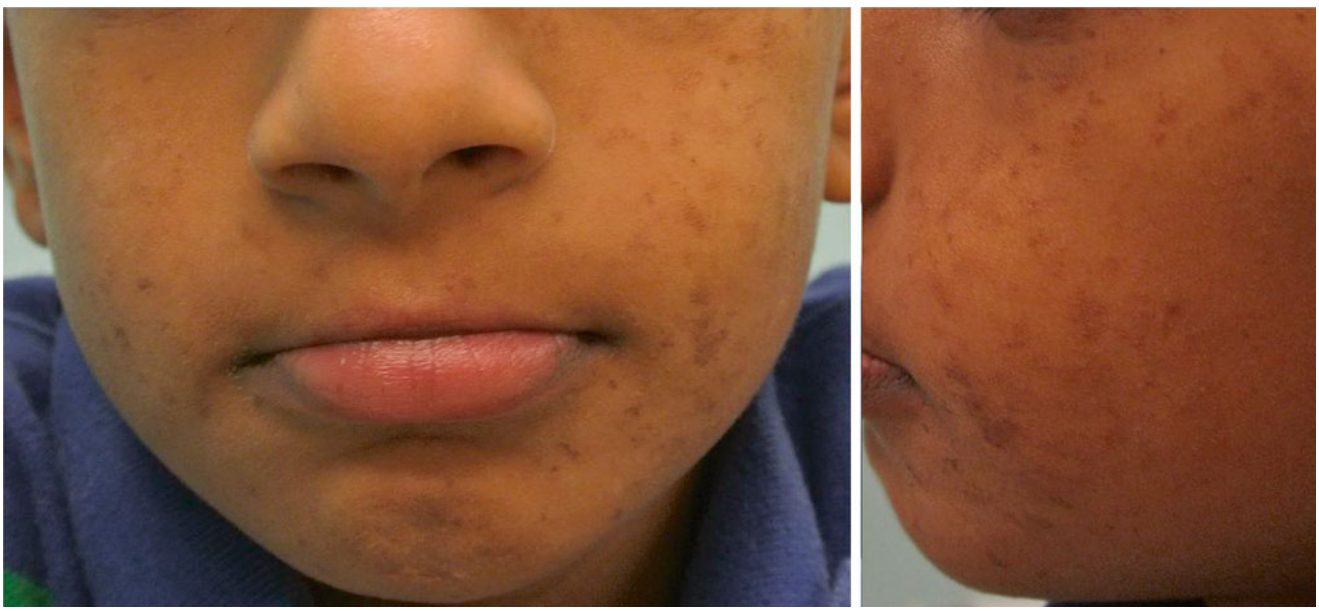

Fig. 23.8 Postinflammatory hyperpigmentation in a child with resolving BCH

features and called it JXG [58]. More recently, the World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations designated it as a dendritic cell-related histiocytic disorder [10].

The pathogenesis of the JXG remains unknown, but a potential role of infectious agents and physical factors has been proposed [41]. More than 70 % of cases present before 12 months of age and 35 % are present at birth [57]. Male patients are more affected with a male:female ratio of 1.4–12:1 [43].

The clinical presentation varies from solitary to multiple lesions or disseminated forms. JXG lesions are described as yellow-brown papules or nodules [59] (Fig. 23.9). JXG have been classified as papular/micronodular and nodular/macronodular. The papular or micronodular type is characterized by multiple, firm, dome-shaped, 2–5 mm lesions, and their color may be initially red-brown, but rapidly become yellowish. The nodular or macronodular variant presents with one or few isolated, nodular, 10–20 mm in diameter, flesh-colored, red, or yellow-brown lesions.

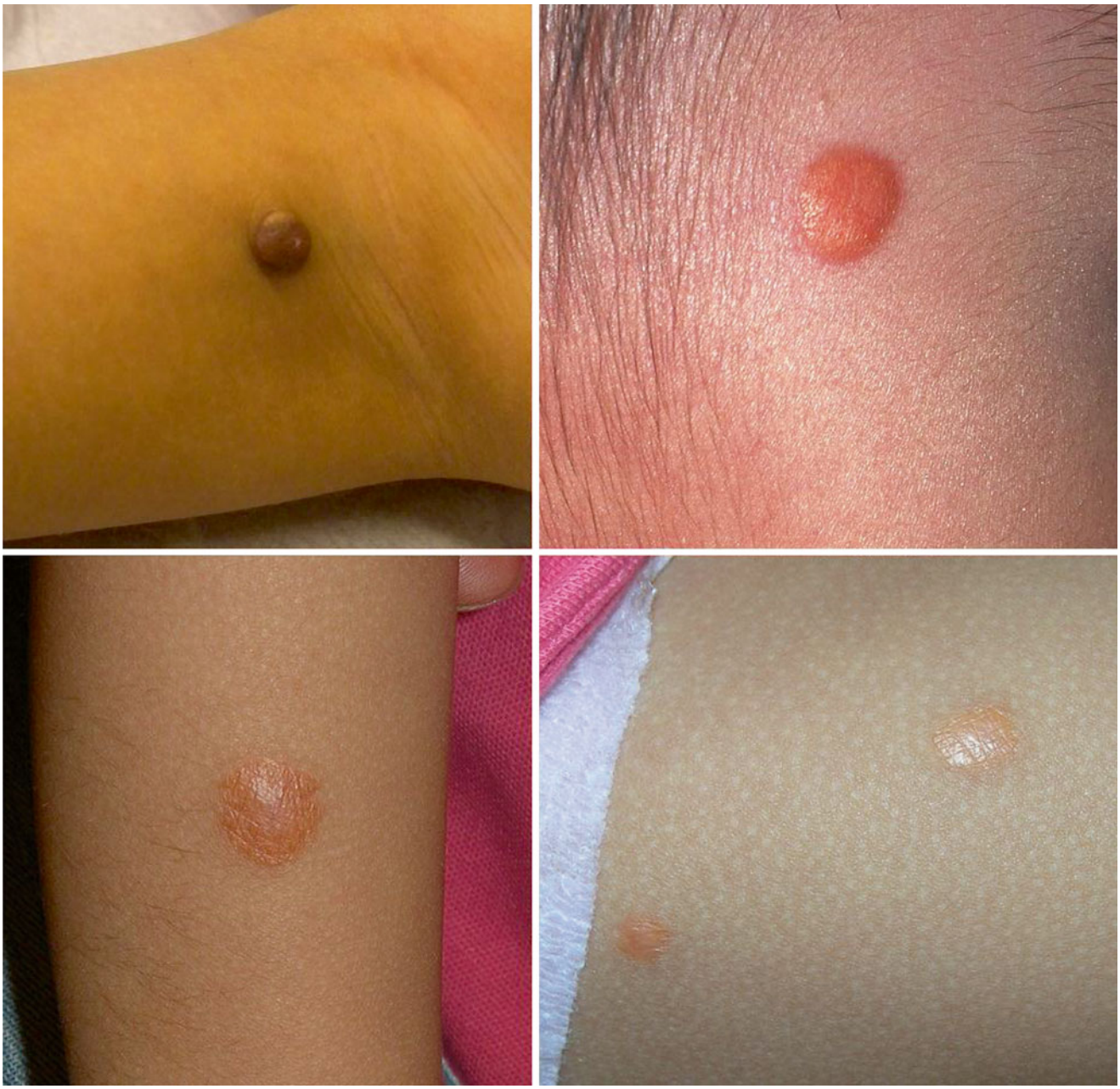

Fig. 23.9 Variety of presentations of JXG. (**a**) *Brown* (hyperpigmented) nodule, (**b**) *yellowish-red* nodule, (**c**) *yellowish-pink* plaque, (**d**) *flesh-colored* plaque

Sometimes telangiectasias of the overlaying skin may also be evident. Although the former variant has been associated with higher risk of presenting extracutaneous lesions (ocular) and the latter with systemic disease, there is not enough evidence to support this theory [59].

In the last few years an increased number of new variants have been described. These variants are:

1. Giant JXG: Presents as nodules or plaques, usually congenital, ranging from 2 to 7 cm in diameter and can be yellow, orange, or red to brown. These grow rapidly during the first few weeks/months and then regress gradually [60] (Fig. 23.10).
2. Mixed or plaque-like: Multiple, uniform, red-yellow to pink-brown nodules and papules in a coalescent pattern [61].
3. Clustered JXG: Similar presentation to plaque-like lesions but made up of numerous small lesions [62] (Fig. 23.11).
4. Multiple lichenoid JXG: Multiple, 1–2 mm in diameter, flat, yellowish-brown lesions with lichenoid appearance) [63] (Fig. 23.12).

JXG present more commonly in the head and neck (40–42.5 %) followed by trunk (26–41 %) and proximal upper extremities (7.9–15 %), but lesions may be seen anywhere in the body [57, 64, 65]. Although the skin can be the only site affected with JXG, infrequently other organs can be involved [65–67]. Eye involvement has been reported as the second most common location and can be affected in the absence of skin lesions. Incidence of ocular involvement among children with cutaneous JXG is around 0.3–0.4 %, while more than 50 % of the patients with ocular JXG may present without skin lesions [57]. Subcutaneous and intramuscular JXG have also been reported with estimated frequencies of 16 % and 14.7 %, respectively [57, 64]. Subcutaneous lesions are usually congenital, measure less than 3 cm, and are most frequently found on the head, whereas intramuscular JXG lesions can be larger than 4 cm and are found in any muscle [59, 64]. Both variants, unlike classic JXG, may present with few or absent Touton cells [59]. Visceral or systemic JXG is an uncommon presentation. It can occur with or without cutaneous involvement. JXG tumors can be associated with higher morbidity and mortality depending on the organ affected. Visceral JXG do not cause symptoms unless large or infiltrative. Mortality in patients with multivisceral JXG has been reported to be as high as 25 % [65, 66].

The diagnosis of JXG is based mainly on clinical manifestations, but clinical diagnosis might be challenging at times. Differential diagnoses include some other histiocytic conditions such as BCH and generalized eruptive histiocytoma (GEH), LCH, reticulohistiocytoma, tuberous xanthoma, Spitz nevus, lymphoma, and other malignant sarcomas [57, 58].

Definitive diagnosis of JXG can be confirmed by histology. The classic findings in the biopsy include well-circumscribed nodules with dense histiocytic infiltrates. Lesions that affect the skin usually involve the dermis. Touton giant cells are

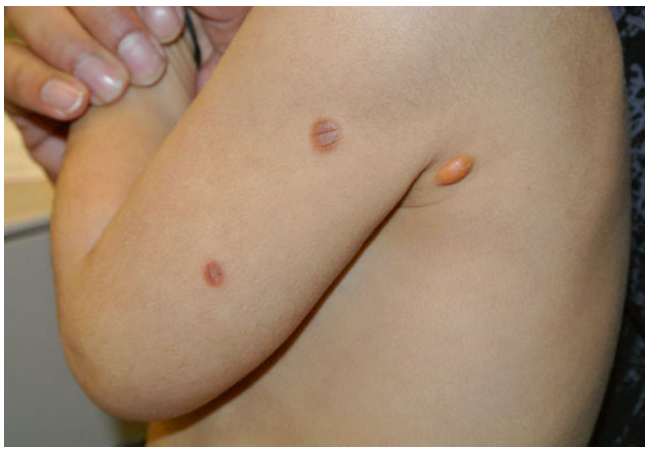

Fig. 23.10 Macronodular JXG presenting with *yellow-brown* and hyperpigmented lesions

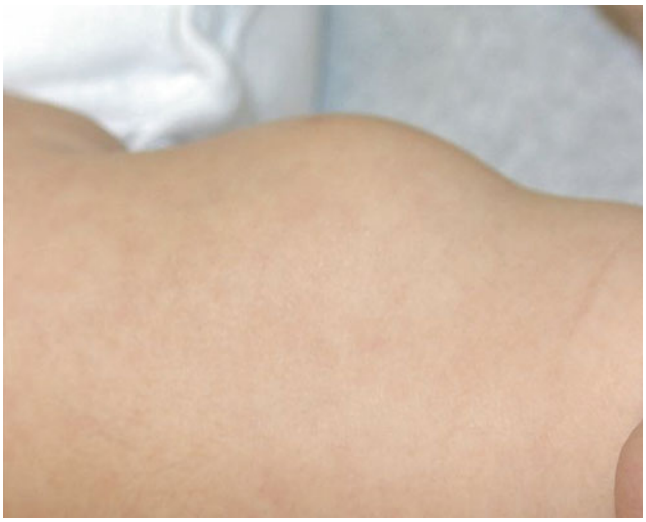

Fig. 23.11 Congenital JXG presenting as a subcutaneous tumor

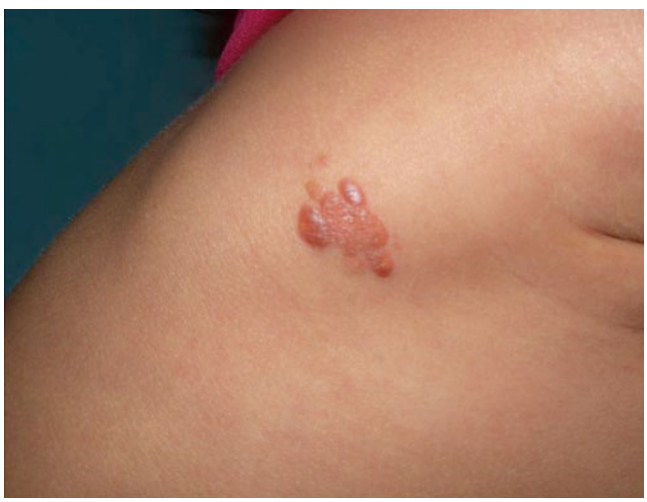

Fig. 23.12 *Pink-brown* nodules and papules in a coalescent pattern seen in lichenoid JXG

pathognomonic, although these are seen only in 85 % of the cases [41]. Early lesions of JXG show non-lipidization of the infiltrate and may have scattered eosinophils, mimicking LCH. Touton-type giant cells are generally absent. Late JXG, also known as transitional, are found in the deep soft tissue and have a storiform (fibro) histiocytic proliferation in a spindle cell area [57]. The cells of histiocytes and giant cell are monocyte-macrophage in origin. These cells typically lack CD1a expression and S-100 and Birbeck granules are negative. Positive stains for Factor XIIIa, HAM, CD68, CD4, CD163, and fascin can be seen [7, 59].

JXG lesions have a benign clinical course and do not required treatment. Lesions typically resolve spontaneously leaving in some cases residual atrophic or hypo- or hyperpigmented scarring. Solitary skin or subcutaneous lesions traditionally have been surgically removed or might be observed while waiting for spontaneous regression (over 1–6 years). In cases with significant symptomatic, multisystemic involvement, chemotherapy regimens used to treat LCH may be effective [56, 68].

Generalized eruptive histiocytoma (GEH) is a rare condition with benign behavior that belongs to of the non-LCH group and affects mainly adults. Few pediatric cases have been reported. Since it was first described by Winkelman and Müller in 1963 [69], more than 31 cases have been reported including 9 pediatric cases. GEH presents as asymptomatic, red-brown to red-blue, or pale erythematous papules and/or nodules. Symmetric distribution is reported and mostly affects the trunk and proximal limbs and less often mucosal surfaces [70]. Lesions also appear in crops without previous local trauma and show tendency to self-resolve. Lucas et al. analyzed eight pediatric cases, and found that GEH lesions presented between 4 months and 9 years of age had a variable time to self-resolve and affected girls and boys equally [71].

Histopathologically, GEH resembles and may be impossible to differentiate from BCH; however the localization and age of presentation of the latter help with the diagnosis [70]. It has been suggested that GEH, JXG, and BCH are the continuous spectrum of the same dendritic cell disorder rather than distinct entities due to their shared immunohistochemistry (S-100–, CD1a–, CD68+, and factor XIIIa+) and clinical characteristics [72]. GEH tends to resolve spontaneously leaving brown pigmentation behind. No treatment is required [69, 70].

Progressive nodular histiocytosis (PNH) is a very rare variant of non-LCH. Affected patients are usually young adults in their third to fourth decades of life, but few pediatric cases have been reported [73]. Patients present with several to hundred yellowish-brown papule/nodules that range from 0.5 mm to 5.0 cm that rarely get mucosal involvement and tend to not have flexural distribution [74]. PNH histopathology has a predominance of storiform spindle-shaped histiocytes confining to the dermis. Because the lesions do not self-resolve, surgical treatment is recommended. Few reports mentioned the use of chemotherapy without success [75].

Cutaneous Non-LCH with Major Systemic Component

Xanthoma disseminatum (XD) is a rare benign histiocytic condition which presents as multiple xanthomas affecting skin and mucosa in otherwise normo-lipemic patients [76]. It was first described by Von Grafe in 1869 and originally thought to overlap with other LCH such as Hand–Schüller–Christian disease [77]. XD mainly presents before the third decade of life (60 %). The age ranges from 9 months to 65 years [78]. It is more frequent on males and the duration of the disease varies from 5 to 28 years [78]. Usually, XD manifests as hundreds of red-brown to yellow discrete papules and nodules. These symmetrically involve face and trunk and affect flexures and folds. Mucosal involvement includes mouth, pharynx, larynx, conjunctiva, and cornea (30–50 %) and can also affect bone marrow, hepatobiliary, musculoskeletal, respiratory, gastrointestinal, and neurological systems [79]. Cutaneous xanthomas and mucosal xanthomas in addition to diabetes insipidus (up to 40 %) form a classical clinical triad [80]. Although XD lesions are benign, involvement of respiratory tract and central nervous system is associated with important mortality and morbidity. Persistent and progressive forms with systemic involvement are common; nevertheless few cases of self-healing forms with spontaneous resolution have been rarely reported. XD and LCH had similar histological findings, but histiocytes in XD do not show the characteristic Birbeck granules in their cytoplasm. These are negative for S-100 and CD34 and positive for CD68. Usually they contain lipid and cholesterol crystals showing irregular scalloped borders [78]. The course of XD is usually chronic and benign, except when obstruction of respiratory system or intracranial space occupying mass is present. Treatment is mainly symptomatic and some regiments include low fat diet, surgical excision, electrocoagulation, cryotherapy, radiation, antimetabolites, anticancer drugs, lipid-lowering agents, and corticosteroids which have shown different degrees of success [79, 81].

Systemic Non-LCH

Erdheim–Chester disease (ECD) is a rare non-LCH disorder with multisystem involvement. It is usually seen in adults and is extremely rare in children, with less than seven cases

reported [82]. ECD has predilection for bone, especially long bones, but also affects skin and other organs (eye, pituitary gland, retro perineum, and lung) [83]. Bone pain, exophthalmos, and diabetes insipidus are frequently seen together, and other common symptoms include cerebellar syndrome, abdominal pain, and skin lesions [82]. Skin lesions present as multiple, yellow to red-brown papules converging into plaques with symmetric distribution (xanthelasma and xanthomas) [84]. Microscopically ECD shows a proliferation of normal histiocytes, small clusters of cells with nuclear grooves, and numerous multinucleated giant cells of the Touton type. These cells are negative for S-100 protein and CD1a [85]. ECD prognosis depends on the extent of the visceral involvement. Multisystemic disease is associated with high mortality rate due to congestive heart failure, lung fibrosis, or renal insufficiency [43]. Although corticosteroids, radiotherapy, chemotherapy, and immunotherapy have been used as treatment options, these have not been shown to be very effective [83].

Indeterminate-Cell Histiocytosis

Indeterminate-cell histiocytosis (ICH) is a rare disorder due to abnormal homing mechanisms of the cutaneous histiocytic/dendritic system. It is characterized by a proliferation of dendritic cells that resemble LC (CD1a+ and S-100+) but lack Birbeck granules [86]. ICH was originally described by Wood et al. in 1985 and since then very few adults and pediatric cases have been described [87]. It clinically manifests as multiple, red to brown papules and nodules distributed mainly over the trunk and extremities [88]. Flores-Stadler et al. reported a pediatric case with bone lesions without skin or systemic involvement [89]. The precise course and prognosis of ICH is not yet determined although in some patients this process has a benign course and resolves spontaneously [87]. There is no standardized treatment for ICH, but surgical removal, chemotherapy, 5 % fluorouracil, thalidomide, pravastatin, and narrowband UVB have been mentioned in the literature [86, 88].

Solitary Histiocytomas with Dendritic Cell Phenotypes

Some cutaneous and extracutaneous lesions with histiocytic and reticulum cell proliferations have been reclassified as solitary histiocytomas. These may present with or without malignant features and represent a challenge to classify [90]. Different phenotypes include solitary epithelioid histiocytoma (reticulohistiocytoma), congenital solitary LC histiocytoma (variant of CS-HRH), and congenital solitary indeterminate-cell histiocytoma among others [90–92].

Clinical characteristics and histology of these lesions may resemble some other histiocytic disorders; therefore, the diagnosis and treatment should be based on location and associated signs of systemic disease [10]. These conditions can present from early childhood to old age and are described as solitary pink to brown nodules that can be crusted or ulcerated. These can also be seen in other parts of the body, including the subcutis and mucosae. Histology varies, but usually presents with a histiocytic immunophenotype with CD68 and CD163 positivity and variable positivity to XIIIa, CD31, and S-100. Birbeck granules may or may not be present [92].

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a group of nonmalignant, but usually deadly conditions, associated with a genetic (primary) and acquired causes (secondary). HLH is characterized by severe inflammation due to unconstrained proliferation of activated lymphocytes and histiocytes that secrete large amounts of inflammatory cytokines. Clinically it presents with fever (high and persistent), bicytopenia (platelets $<100\times109$/L, neutrophils <109/L), hepatitis, and splenomegaly [93].

Genetic HLH may have an autosomal recessive or X-linked transmission and includes familiar HLH (HLH is the only manifestation of the disease) and immune deficiency syndromes associated with pseudo-albinism (Chédiack–Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome) [9, 94]. Familiar HLH (F-HLH) incidence is about 1 in 50,000 live births; it is found almost exclusively in childhood, and has a slight male preponderance [95].

Acquired forms of HLH can present at any age and are more common than genetic cases. Several infectious organisms [96], malignant disorders (lymphoma, leukemia of peripheral T or NK cell lineages), and rheumatologic diseases have been associated with its onset [94]. Cutaneous manifestations found in patients with HLH are not specific and many different morphologies have been described (purpuric, macular, papular, erythrodermic, and morbilliform). Skin involvement may be present in about 43 % of cases in early stages and in up to 65 % at later stages of the disease [97]. HLH treatment consists of combinations of immunosuppressive therapy and pro-apoptotic chemotherapy (HLH-94/HLH-2004) and treatment has reduced mortality associated with HLH from 95 % to 30–35 % [93].

Rosai–Dorfman Disease

Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai–Dorfman disease (RDD) is a benign, rare, histiocytic proliferative disorder of unknown etiology. It presents as painless cervical lymphadenopathy with or without extranodal manifestations [98]. Rosai and Dorfman described and published this condition for the first time in 1969 [99]. It mainly affects children and young adults under the age of 20 years and its male-to-female ratio is 1.4:1 [100]. Infectious agents such as Epstein–Barr virus or herpes simplex virus have been mentioned as possible pathogenic agents [98, 99]. Up to 90 % of the patients present with bilateral, massive cervical lymphadenopathy not associated with pain [101]. Patients at presentation may also present with fever, night sweats, malaise, weight loss, leukocytosis, neutrophilia, and elevated erythrocyte sedimentation rate; therefore it is important to differentiate it from Hodgkin's disease of the neck [100]. About 10 % of affected patients may develop cutaneous manifestations such as asymptomatic xanthoma-like, yellowish or reddish-brown papules, nodules, or plaques that may or may not ulcerate [102]. Extranodal disease affects up to 40 % of patients, and the most frequently involved locations are head and neck and upper respiratory and digestive systems. Although rare, involvement of orbits and CNS has been reported in children [101]. Fine-needle aspiration cytology (FNAC) from cervical node is a reliable and useful tool for the diagnoses of RDD. Histology shows abundant and large histiocytes with copious cytoplasm and contrary to what happens during phagocytosis, where lymphocytes are digested by enzymes, the phagocytosed lymphocytes (emperipolesis) appear intact. Unlike other non-LCH conditions, histiocytes in RDD are strongly positive for S-100, negative for CD1, and variable positive for CD68 but lack Birbeck granules [98]. The clinical course of the disease is usually self-limited. Up to 70–80 % of patients have a spontaneous resolution of their disease, but it can also have a chronic course [99]. There is no specific treatment for RDD, but miscellaneous agents such corticosteroids, chemotherapy, and combination of vinca alkaloids and alkylating agents, low dose interferon, radiation therapy, and surgery have been reported effective [102].

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MRH) is a rare histiocytic multisystem disorder presenting with cutaneous nodules and destructive osteoarthropathy. It is most commonly seen in older adults, mostly women, but pediatric cases have also been reported [43]. Etiology of MRH is unknown; however, some cases have been associated with malignancies and autoimmune diseases (30 % and 20 %, respectively) [103, 104]. MRH can involve the skin, joints, and mucosae; and other organ systems may also be affected. Typically the presenting symptom is arthritis, which is symmetric and affects small and large joints, and rapidly progresses to destruction and deformity of joints [105]. Cutaneous findings may precede the arthritis in 18 % of cases or be seen simultaneously with the arthritis in up to 21 % of patients. The skin can present solitary or multiple, coalescing, tender papules or nodules (cobblestone appearance). Lesions can vary in size from few millimeters to 2–3 cm and can also have different colors (skin colored to reddish-brown). Common affected locations are face, scalp, and dorsum of the hands, lateral aspect of fingers, periungual (coral beads), elbows, neck, trunk, and soles [104]. Histological findings from skin and synovial fluid show characteristic multinucleated giant cells with fine granulated, ground glass appearance of the eosinophilic cytoplasm. Histiocytes are CD68 positive but CD3, CD19, CD20, S-100, and CD1a are usually not reactive [103]. The course of the disease varies from spontaneous resolution to aggressive, deforming and mutilating disease. There are no guidelines of treatment for MRH. Nonsteroidal anti-inflammatory drugs (NSAIDs) corticosteroids, etanercept, methotrexate, and cyclophosphamide have been used to treat patients [106, 107].

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Transient Neonatal Pustular Melanosis

24

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Abstract

Transient neonatal pustular melanosis (TNPM), an idiopathic dermatitis largely observed in full-term neonates with skin of color, has distinctive features characterized by small vesicles and pustules that rupture easily, leaving collarettes of scaling and hyperpigmented macules. Although clinical presentation or stage may vary, the lesions of TNPM are distinctively present at birth and may manifest anywhere on the body, including the palms of the hands and soles of the feet. The initial lesions usually disappear spontaneously within the first 2 weeks of life without long-term sequelae, and no treatment is required.

Keywords

Neonatal pustular melanosis • Idiopathic dermatitis • Vesicles • Pustules • Collarettes • Scaling • Hyperpigmented

Overview

Transient neonatal pustular melanosis (TNPM), an idiopathic dermatitis largely observed in full-term neonates with skin of color, has distinctive features characterized by small vesicles and pustules that rupture easily, leaving collarettes f scaling and hyperpigmented macules [1–4]. Although clinical presentation or stage may vary, the lesions of TNPM are distinctively present at birth and may manifest anywhere on the body, including the palms of the hands and soles of the feet [3, 5, 6]. The initial lesions usually disappear spontaneously within the first 2 weeks of life without long-term sequelae, and no treatment is required [2–4, 7, 8].

Historically, this condition was grouped with vesicular and bullous lesions and termed "pemphigus neonatorum" [1]. It was not described as a distinct entity until 1976 [4], although it may have been recognized as early as 1961 and identified as "lentiginosis neonatorum" at the time [9].

Epidemiology

TNPM is a benign, asymptomatic, self-limited skin eruption with no associated mortality or morbidity [1–4]. Infants with this condition may eventually develop classic erythema toxicum neonatorum (ETN), but few infants with TNPM have other neonatal rashes [3]. However, the relationship between TNPM and

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ETN remains unclear [10]. TNPM is not associated with any systemic manifestations [11].

TNPM is a rare disorder with a worldwide prevalence in newborn infants of less than 1 % [3, 4, 12]. Few observations of significant numbers of screened infants have been reported in the literature. Previously published incidence rates for TNPM in the United States have ranged between 0.1 % [6] and 0.6 % [4] in Caucasian infants and between 4.4 % [4] and 5.0 % [6] in African-American infants, while the overall incidence rate has ranged between 0.2 % [8] and 2.2 % [4]. TNPM is more common in term-gestation infants [13], and occurs equally in both genders [5]. It has also been reported in non-African-American infants with skin of color, although published reports are scarce. TNPM can be observed in all racial groups, especially those with darker constitutive pigmentation, such as Latin Americans [2, 8], South Asians [14–16], and those of Mediterranean or Middle Eastern origin [17, 18].

Summary Points

- TNPM is a benign, asymptomatic, self-limited dermatitis with no associated mortality, morbidity, or systemic manifestations.
- TNPM predominantly affects black neonates, in whom the incidence is the highest.
- Although it has been observed in all racial groups, TNPM primarily occurs in infants with darker constitutive pigmentation.

Clinical Presentation

TNPM is characterized by clustered vesicles, superficial pustules, and hyperpigmented macules [1–4]. Evidence of self-resolving lesions, including white collarettes and postinflammatory hyperpigmentation, are often present along with the pustules, especially in infants with naturally pigmented skin [4].

The primary lesions generally progress through three stages of development. Initially, lesions appear as rather uniform, round, 2- to 4-mm pustules without surrounding erythema on a background of healthy skin [3, 18, 19]. These are not clear vesicles; rather, they contain a milky, purulent exudate. The areas of the body most frequently affected include the forehead, temporal regions, cheeks, neck, back, and buttocks; although rare, involvement of the palms and soles has also been reported [4, 19]. Because of their fragile nature, the superficial pustules rupture easily and are often missed because they are wiped off easily in the delivery suite when the newborn is cleansed of vernix. Intact pustules may persist for several days

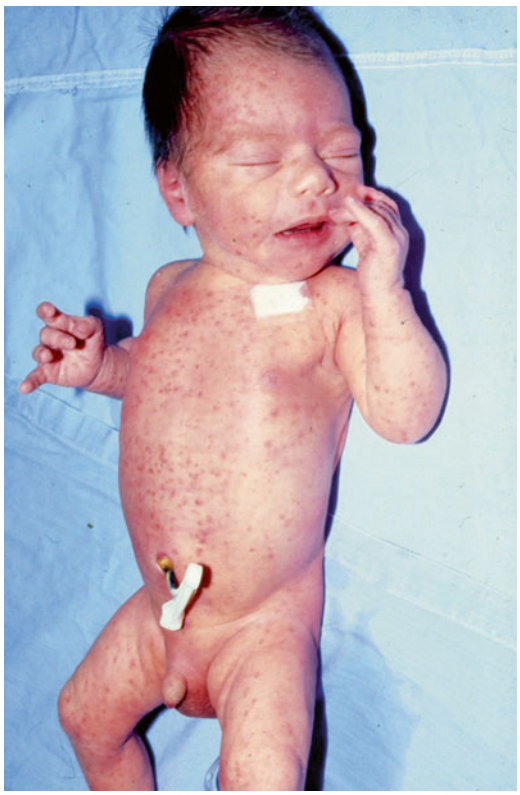

Fig. 24.1 Pustules and denuded lesions with residual discoloration in a Mexican infant (photo courtesy of Carola Duran McKinster)

in more protected areas, such as beneath the chin, in the axillae, in the groin, or in the inner thighs, and on thicker areas of skin, such as the knees or palms [2, 14, 15]. New lesions do not occur after birth [3].

Next, the vesicles and pustules may desquamate during the neonate's first bath, leaving characteristic, delicate collarettes of thin white scale around the perimeter of each denuded pustule and brown hyperpigmented macules (Fig. 24.1). Skin findings can be correlated with gestational age at birth. Near-term neonates, especially those delivered by cesarean section, may exhibit just the unbroken pustules. Term or post-term infants may have only macules remaining, frequently with the telltale collarette of flaking epidermis, which suggests that the pustular phase may have occurred in utero.

Lastly, within hours of exposure to the atmospheric environment, the central hyperpigmented brown macule becomes apparent [4]. Macules are round, have smooth and distinct borders, and may frequently be confused for freckles. They may be profuse or sparse and are commonly found under the chin and on the neck, upper chest, back, and buttocks. Sometimes, the palms, soles, and scalp are affected.

No systemic signs or symptoms are associated with the skin lesions of TNPM [6, 15]. The vesicopustules typically disappear within 24–48 h of birth [3, 4, 7, 8]. The hyperpigmented melanotic macules usually fade spontaneously over the course of 3–4 weeks, although full resolution may occasionally take several months [3, 5]. The etiology of TNPM remains unknown. No familial predisposition has been identified for TNPM. Increased frequency of placental squamous metaplasia has been reported in the mothers of some infants, although this relationship has not been demonstrated in any large clinical trial [20].

Summary Points

- TNPM is characterized by small clustered vesicles and superficial pustules that rupture easily, leaving collarettes of thin white scale and brown hyperpigmented macules.
- The skin lesions of TNPM are not associated with any systemic signs or symptoms.
- The vesicopustules generally disappear within 24–48 h of birth; the brown macules fade spontaneously within 3–4 weeks, although full resolution may take several months.

Diagnostic Evaluation

The diagnosis of TNPM is usually made by clinical examination [3, 5]. If the clinical presentation is typical of TNPM (i.e., vesiculopustular lesions with hyperpigmented macules present at birth), a full diagnostic workup is generally not indicated. Conversely, if appearance is not typical, cytologic and histologic investigations are warranted to rule out other vesiculopustular dermatoses that can be the presenting features of serious infectious, inflammatory, or genetic neonatal disorders [3]. Thus, it is important to rapidly and confidently differentiate between benign and serious conditions (Table 24.1), so as to take immediate and effective action should the need arise. The goal of this diagnostic approach is to spare a healthy neonate with TNPM either potentially harmful antibiotic or antiviral therapy, an invasive evaluation for sepsis, or prolonged hospitalization, all of which have their own inherent morbidity [5].

In a neonate with TNPM, a Tzanck smear with a cellular stain (e.g., Wright–Giemsa stain) or Gram stain of the contents of a pustule reveals a predominance of large quantity of neutrophils and occasional eosinophils and cellular debris [5,

Table 24.1 Differential diagnosis of neonatal vesiculopustular dermatoses by etiology

Dermatosis	Clinical presentation	Diagnostic test	Cytologic/histologic results
Noninfectious disease			
EPF	Crops of papules, vesicles, and pustules that crust, predominantly on scalp with some lesions on the trunk and extremities	Tzanck smear	Eosinophils and neutrophils
		Gram stain	No bacteria
ETN	Red macules and papules; white to pink pustules; vesicles on the face, trunk, and extremities	Tzanck smear	Abundant eosinophils, rare neutrophils
		Gram stain	No bacteria; abundant eosinophils
Incontinentia pigmenti	Linear irregular vesicular and bullous lesions (rarely pustular) over the trunk and extremities	Tzanck smear	Abundant eosinophils
		Biopsy	Intraepidermal eosinophilic spongiotic pustules; dermal infiltrate with many eosinophils mixed with lymphocytes in an extrafollicular location
Infantile acropustulosis	Red papules evolving into pustular and vesicular lesions within 1 day	Tzanck smear	Eosinophils predominate early on; neutrophils predominate later on
		Gram stain	No bacteria
		Biopsy (rare)	Intraepidermal vesicles early on; subcorneal pustules (mostly PMN leucocytes); mild perivascular infiltrate
Neonatal acne	Closed comedones mainly; open comedones, papules, and pustules in the face	Gram stain	Bacteria and yeast cells
		Culture	Bacteria (*Staphylococcus epidermidis*, *Propionibacterium acnes*) and yeasts (*Pityrosporum ovale*)
Pustular miliaria	Generalized grouped erythematous papules and pustules with an increase in the intertriginous areas	Tzanck smear	Lymphocytes predominate
		Gram stain	No bacteria

(continued)

Table 24.1 (continued)

Dermatosis	Clinical presentation	Diagnostic test	Cytologic/histologic results
TNPM	Vesicles and pustules desquamate leaving brown macules on chin, neck, palms, and soles	Tzanck smear	Abundant neutrophils, rare eosinophils
		Gram stain	No bacteria; neutrophils, rare eosinophils
		Biopsy (rare)	Intra- and subcorneal pustule composed nearly entirely of neutrophils; rare dermal infiltrate
Infectious disease			
Candidiasis	Pink to red macules and papules evolving into pustules and vesicles	KOH preparation	Pseudohyphae and spores
		Culture	*Candida albicans* isolated
Herpes simplex	Grouped or single vesicles on erythematous bases in crops on the skin and mucous membrane	Tzanck smear	Multinucleated giant cells
		Direct IF	Positive for HSV
		Culture	Growth of HSV
		PCR	Identification of HSV DNA
Impetigo bullosa	Vesicles, pustules, and bullae on an erythematous base in the neck, axilla, groin, and diaper area	Tzanck smear	Neutrophils and bacteria
		Gram stain	Gram-positive cocci in clusters and neutrophils
		Culture	*Staphylococcus aureus* isolated
Pityrosporum folliculitis	Follicular papules and sparse pustules on the face and scalp	KOH preparation	Monopolar yeast cells bud with a broad base
		Culture	*Pityrosporum ovale* isolated
Scabies	Vesicles, pustules, and papules; rare burrows on the hands, feet, trunk, and genitalia	KOH or mineral oil preparation	*Sarcoptes scabiei* mites, eggs, or fecal particles

7, 21]. No evidence of bacterial, yeast, or viral infection is found. Gram stain preparations for bacteria are negative, so are blood test results and skin culture findings. Vesicopustules show intracorneal and subcorneal collections of neutrophils with occasional eosinophils, mild acanthosis, and some intraepidermal edema. Occasionally, fragmented hairs may be seen in the blister cavity. Dermal inflammatory infiltrate is minimal. Pigmented macules reveal a basket-weave, slightly hyperkeratotic stratum corneum [4] along with hypermelanosis in the epidermal basal cells, but no melanin in the dermis [20, 22].

DNA deoxyribonucleic acid, *EPF* eosinophilic pustular folliculitis, *ETN* erythema toxicum neonatorum, *HSV* herpes simplex virus, *IF* immunofluorescence, *KOH* potassium hydroxide, *PCR* polymerase chain reaction, *PMN* polymorphonuclear, *TNPM* transient neonatal pustular melanosis. Adapted from [3] and [5].

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Clear Cell Papulosis

25

Nanette B. Silverberg

Abstract

Clear cell papulosis is a rare condition in which white, flat-topped papules arise in the mammary line bilaterally, usually over the lower abdomen. Asian females seem to account for the majority of the cases reported in the literature. Onset is in childhood and these lesions are believed to be remnants of mammary glandular secretory cells, being histologically AE1 positive and CAM 5.2 positive.

Keywords

Papulosis • Papules • Mammary • Glandular secretory cells • Cluster

Introduction

Clear cell papulosis is a newer entity, first described in 1987 [1]. It is a rare condition in which white papules arise and cluster in the mammary line bilaterally, usually over the lower abdomen and pubis [2]. Onset is in childhood and these lesions are believed to be remnants of mammary glandular secretory cells, having large clear Pagetoid cells within the lesions which are AE1 positive and CAM 5.2 positive [2]. Lesions seem to spontaneously resolve with age.

Epidemiology

- **Rare entity with about two dozen reported cases**
- **Familial component, three sets of twins have been reported with clear cell papulosis**
- **Largely reported in Asia**

Only a few dozen cases of clear cell papulosis have been described. It is a rare entity, noted primarily in Asian girls, with reports initially out of Taiwan [2]. More recent reports have come from Singapore, the United States (including Asian and Hispanic children), and India [3–7] and the entity has been reported in Asians, Hispanics, and has a familial component with siblings often affected [4]. The entity may occur in Asian and Hispanic populations worldwide (Fig. 25.1).

Clinical Features/Diagnosis

- **White papules along the mammary line.**
- **Clustered lesions usually over the lower abdomen and pubis, but can be placed anywhere along the milk line.**
- **Lesions can be subtle and biopsy with special stains will aid in the identification of pagetoid clear cells.**

Multiple white papules can be located over the lower abdomen and pelvis in areas of mammary line development. Clustering can occur. Placement may be any place along the mammary line including the axillae, upper chest, and back (Fig. 25.1) [7]. Lesions can appear lichenoid or imperceptibly elevated.

Histology reveals benign pagetoid clear cells in the basal layer of a hypomelanotic acanthotic epidermis. Cytoplasmic mucin is noted and lesions are positive for anticytokeratin antibodies (AE1/AE3), cell adhesion molecule (CAM) 5.2 [3],

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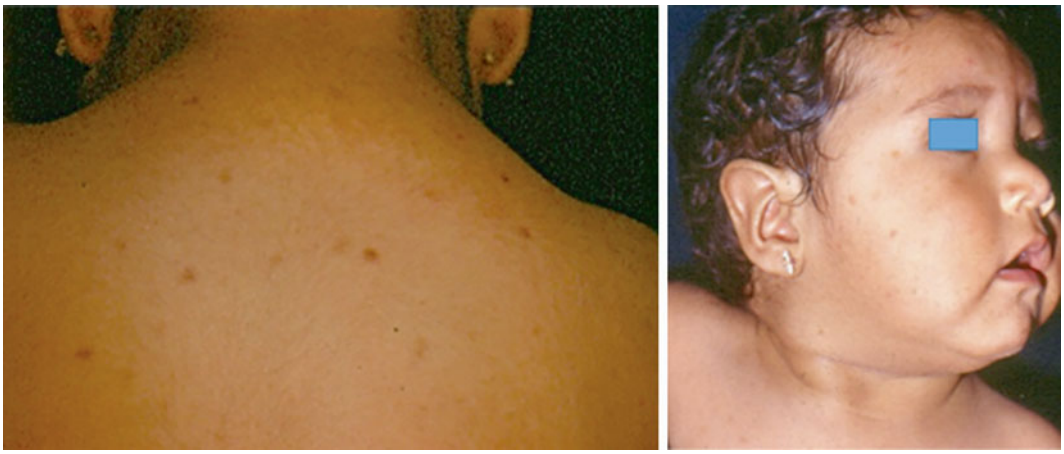

Fig. 25.1 Clear cell papulosis. Courtesy Prof. Ramón Ruiz-Maldonado

cytokeratin 7, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA). The cells also stain with mucicarmine, colloidal iron, alcian blue (pH 2.5), and periodic acid-Schiff. S100 staining is negative [3] and BRST2 is positive [6]. The cells are presumed to be of sweat gland origin and may be derived from Paget cells or Toker cells [4, 5, 7].

The differential diagnosis includes acquired hypomelanoses including chicken pox scars, idiopathic guttate hypomelanosis, hypomelanotic tinea versicolor, anetoderma, and early, hypopigmented lesions of Paget's disease [2]. Clear cell papulosis may also be construed as normal on skin biopsy and multiple biopsies or biopsies with a rim of surrounding skin may be necessary [7, 8].

Treatment

No treatment is needed. A recent case series following 19 Taiwanese patients with clear cell papulosis showed gradual resolution over a median of 11.5 years for all patients and complete clearance in 85.7 % [9]. Clear cell density was reduced in 1 patient even when full clearance was not achieved. Parental reassurance can be given in these settings.

Research

None was identified in the literature at this time.

Conclusions

Clear cell papulosis is a newer entity which appears to be benign developmental deposition of breast-derived cells in the epidermis along the milk lines. No therapy is required as most cases spontaneously resolve with time.

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Vascular Tumors/Birthmarks

26

Francine Blei and Bernardo Gontijo

Abstract

"Vascular anomalies" encompass a heterogeneous group of vascular lesions, of unclear etiology and often with unpredictable behavior. Patients with vascular anomalies represent a unique population, in that they have focal (or generalized) aberrations of vascular development (in vascular malformations) or vascular proliferation (in vascular tumors). The etiology of these disorders is yet unclear, and likely represents a multifactorial process, although new discoveries into the genetic and molecular bases of these disorders have dominated the past decade.

Keywords

Hemangioma • Birthmark • Vascular anomaly • Propranolol

Introduction

Vascular anomalies are classically divided into two fundamental categories, based on their tendency to proliferate. Classification systems importantly specify accepted terminology and provide a format for diagnosis, management, and research. Early detection, proper evaluation, and appropriate diagnosis are essential, as these entities are medically very different. The most recent classification was last updated by the 1996 Workshop of International Society for the Study of Vascular Anomalies (ISSVA), amplifying the more elementary previous classification proposed by Mulliiken and Glowacki, to include histologic and rheologic features, new subcategories of diagnoses, and updated histologic, genetic information and syndromes (Table 26.1). These distinctions provide a framework to provide a common nomenclature and distinguish vascular anomalies into functional and descriptive categories enabling optimal assessment and treatment for patients [1, 2]. An updated classification was approved at the ISSVA 20th International Workshop, April, 2014, which incorporates newly recognized entities, syndromes and genetic and histologic knowledge.

The focus of this chapter will be on hemangiomas of infancy (HI), as epidemiologic and ethnic-specific data, albeit limited, are most available for this subgroup. The growth curves and typical clinical and molecular features of "typical hemangiomas" are depicted in Fig. 26.1 [3]. North and colleagues identified robust staining for the Glucose transporter 1 protein (GLUT1) in any growth stage of typical hemangiomas (and not expressed in other vascular anomalies), which is of diagnostic utility [4].

Figure 26.2 depicts the time- and size-related variation in clinical presentation and behavior of the three types of hemangiomas (common hemangioma of infancy, rapidly involuting congenital hemangioma, and non-involuting congenital hemangioma). In-depth reviews comparing the various forms of hemangiomas are provided in recent reviews by Léauté-Labrèze, Hoeger, and Luu and colleagues [5–7].

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Table 26.1 ISSVA classification for vascular anomalies© (Approved at the 20th ISSVA Workshop, Melbourne, April 2014)
Overview table

	Vascular malformations			
Vascular tumors	Simple	Combined[a]	of major named vessels	associated with other anomalies
Benign	Capillary malformations	CVM, CLM	See details	See list
Locally aggressive	Lymphatic malformations	LVM, CLVM		
or borderline	Venous malformations	CAVM[b]		
Malignant	Arteriovenous malformations[b]	CLAVM[b]		
	Arteriovenous fistula[b]	Others		

[a]Defined as two or more vascular malformations found in one lesion
[b]High-flow lesions
N.B. The classification tables do not list exhaustively all known vascular anomalies. Some rare "dermatologic" vascular anomalies will be found in dermatology textbooks
The tumor or malformation nature or precise classification of some lesions is still unclear
These lesions appear in a *separate provisional list*
For more details please refer issva.org/classification
This is an updated version of the classification described by Enjolras, O et al. Color Atlas of vascular tumors and malformations. Cambridge University Press; 2006 [2]

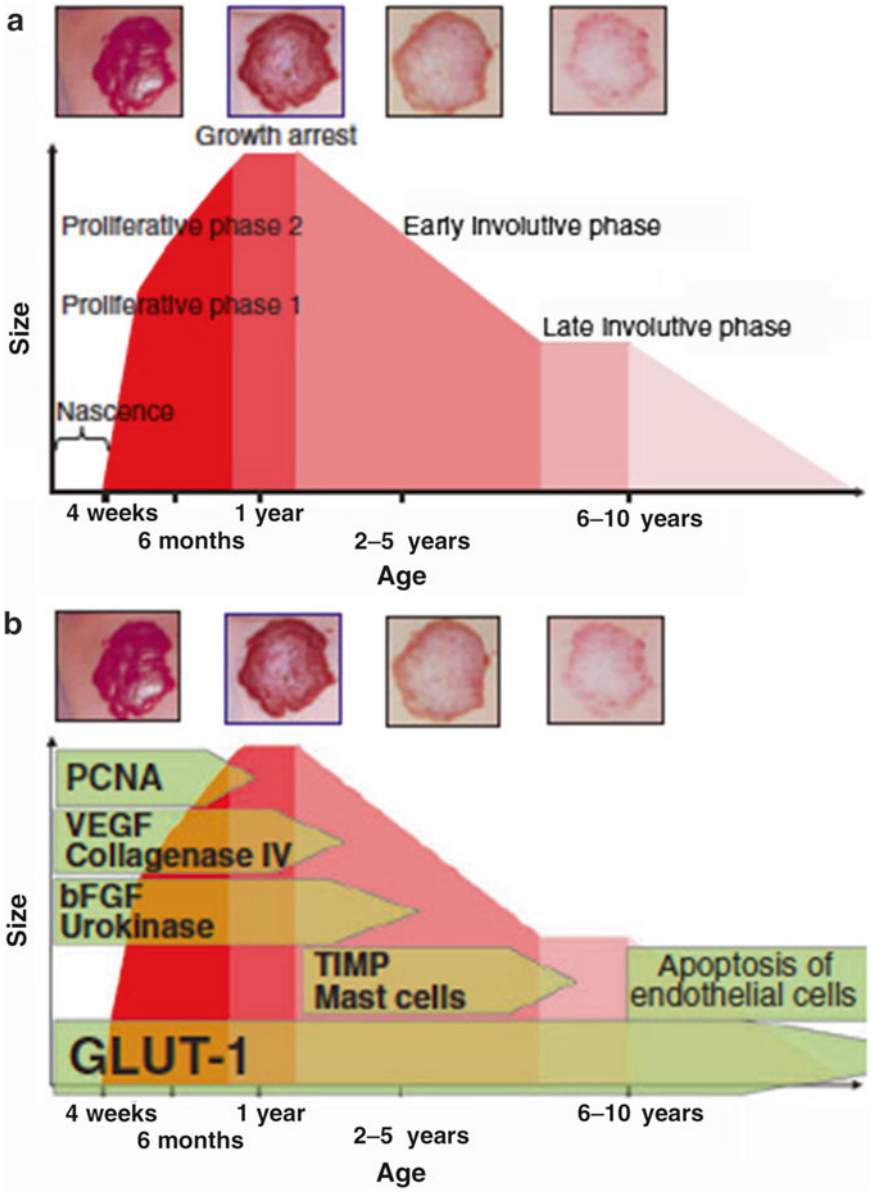

Fig. 26.1 Growth phases and properties of hemangioma of infancy. (**a**) Growth and regression of infantile hemangiomas (IH). (**b**) Molecular markers characterizing individual phases of IH. *PCNA* proliferating cell nuclear antigen, *VEGF* vascular endothelial growth factor, *bFGF* basic fibroblast growth factor, *TIMP* tissue inhibitor of metalloproteinases, *GLUT-1* glucose transporter type1 ([3], #513)

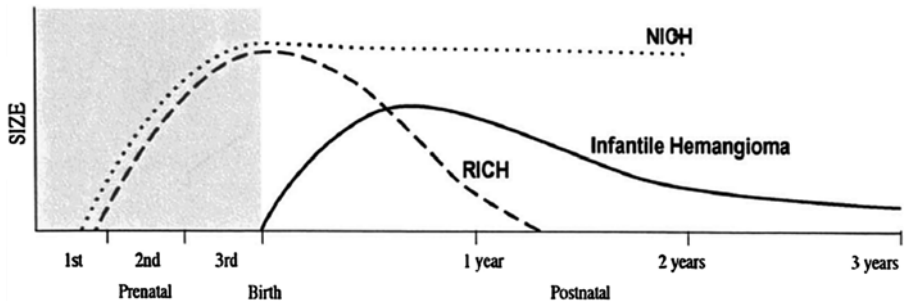

Fig. 26.2 Growth curves of hemangioma of infancy, rapidly involuting congenital hemangioma (RICH), and non-involuting congenital hemangioma (NICH)—note that only hemangiomas of infancy are GLUT1 positive ([8], #389)

Epidemiology

- **Few studies addressing racial/ethnic differences of HI**
- **Predominance in Caucasian infants**
- **Female gender, prematurity, and low birth weight are common risk factors**

Prior to the 1980s, the word "hemangioma" was widely and loosely employed to encompass different vascular disorders. The classification proposed by Mulliken and Glowacki in 1982, and currently adopted with minor alterations, has changed considerably the nomenclature of vascular anomalies [1]. In addition, new categories for race/ethnicity have been created. As such, caution should be exerted in interpreting data originated from former publications. For instance, a large cohort study from 1983 groups salmon patches, stork bites, and Port wine stains under the heading of "capillary hemangioma," with a resulting high incidence of hemangiomas [9].

The first study to estimate the occurrence of HI in different racial groups is credited to Pratt, in 1953 [10]. His patients were classified as either whites, negroes, or part negroes (sic), and "strawberry marks" were equally detected in 1 % of individuals of both groups. Very few reports approaching the occurrence of HI in different ethnic and racial groups have been published ever since (Table 26.2).

Several country-specific studies report neonatal incidences of 0.17–1.3 % for "hemangiomas." However, ascertainment in the immediate newborn period likely represents underreporting and/or erroneous diagnosis, as these studies lack longitudinal follow-up and diagnosis confirmation [22–24].

Due to the peculiar natural history of HI, discrepancies in prevalence/incidence rates in different studies are explained by distinct follow-up periods and timing of examination. Kilcline and Frieden, critically reviewed the literature and acknowledged methodological shortcomings in nomenclature and timing of these studies (i.e., studies in the newborn period may underestimate the true incidence of hemangiomas) [25]. However, these authors proposed that "the incidence is lower than the oft-cited 10 %, and likely closer to 4–5 %," which was later corroborated by Kanada et al. who conducted a longitudinal study of nearly 600 infants in Southern California, with reported hemangiomas of infancy (HI, RICH, and NICH) in 4.9 % (4.5 % incidence of hemangiomas by 3 months of age), 45 % Caucasian, 25 % Hispanic, 4.7 % African-American, 9.4 % Asian, and 14.2 % "Other," 12.1 % born preterm (<37 weeks gestational age), and 5.5 % twins [20]. These authors, who also recognized nevus simplex in 83 % and 0.3 % capillary malformation in their cohort, compared their results to those of several international studies. A longitudinal Australian study of >1,000 infants reported a 2.6 % incidence of infants who developed hemangiomas (confirmed by physicians) during the first 3–6 weeks of life, the majority female (5:1), of low birth weight (10 % <2,500 g), born at a gestational age <37 weeks, and conceived via in vitro fertilization (6.5 %)—although statistically this was not an independent risk factor. In this study, as in others, the majority of affected infants were Caucasian. Limitations include a low overall response rate to this questionnaire-based study (although the data was collected from >1,000 mothers), and the exclusion of very premature and very low birth weight infants [18]. Further, larger, and properly designed studies are needed to determine accurately the frequency of HI in different racial/ethnic groups.

It is postulated that HI predominate in fair-skinned patients and are relatively rare in dark-skinned ones. In the Netherlands, with a heavily predominant light-skinned population, prevalence rates of 9.9 % are reported, with 86 % of affected children being Caucasian [21]. In the USA, most likely the prototype country for multiracial population and ethnicity diversity, the occurrence of HI has been reported to be higher in white non-Hispanic [26]. A possible explanation is that the rise in preterm and low birth weight infants, two well-known risk factors for HI, has been more dramatic in the white non-Hispanic group [27]. A longitudinal Australian study of >1,000 infants reported a 2.6 % incidence of infants who developed hemangiomas (confirmed by physicians) during the first 3–6 weeks of life, the majority female (5:1), of low birth weight (10 % <2,500 g), born at a gestational age <37 weeks,

Table 26.2 Reported incidence of hemangiomas in various ethnic groups

Study	Year	Country	Number of patients	Race/ethnicity[a]	Nomenclature	Timing of examination	Incidence/prevalence
Pratt [11]	1953	USA	1,096	Whites, Negroes, or part Negroes (sic)	Strawberry mark	First 8 days	1 % for both groups
Hidano et al. [12]	1986	Japan	5,387	NS	Strawberry mark	First 14 days	1.7 %
Rivers et al. [13]	1990	Australia	420	Caucasian, Mongolian, Australasian, unknown	None	First 7 days	None
Kahana et al. [14]	1995	Israel	1,672	Jewish, Arab	Strawberry hemangioma	First 4 days	1.3 % Jewish 1.48 % Arab
Navas et al. [15]		Spain	1,027	NS	Other angiomas	First 14 days	3.4 %
Boccardi et al. [16]	2007	Italy	620	European, Asian, North-African, South-American, other	None	First 3 days	None
Shih et al. [17]	20007	Taiwan	500	NS	Hemangioma	First 2 days	0.2 %
Dickison et al. [18]	2011	Australia	1,065	Multiple[b]	Infantile hemangioma	First 6 weeks	2.6 %
Monteagudo et al. [19]	2011	Spain	1,000	White, Roma, Latin American, other	Hemangioma	First 3 days	0.9 %
Kanada et al. [20]	2012	USA	594	Caucasian, Hispanic, African-American, Asian, other	Infantile hemangioma	First 9 months	6.2 % Hispanic 5.4 % Asian 4.5 % Caucasian 3.4 % African American 2.4 % other
Hoornweg et al. [21]	2012	Netherlands	2,204	Caucasian, non-Caucasian	Infantile hemangioma	2 year follow-up	9.9 %

NS not specified
[a]As mentioned in the report
[b]Caucasian, Chinese, Korean, Vietnamese, Indian, and Pakistan, Filipino, other Asian, Mediterranean, Middle Eastern, African, Aboriginal, Polynesian, South American, mixed, other

and conceived via in vitro fertilization (6.5 %)—although statistically this was not an independent risk factor. In this study, as in others, the majority of affected infants were Caucasian. Limitations include a low overall response rate to this questionnaire-based study (although the data was collected from >1,000 mothers), and the exclusion of very premature and very low birth weight infants [18]. Females are markedly more affected than males, with ratios of up to 5:1. When only preterm infants are considered, the incidence of HI during the first year of life is 12.7 % [28]. Low birth weight (<2,500 g) is considered the most important risk factor for developing HI [27].

The Hemangioma Investigator Group, in a study of >1,000 infants, did not, however, provide an overall incidence of their cohort; they reported that hemangiomas of infancy were more likely seen in the following groups: female, white non-Hispanic (68.9 % vs. 14.4 % Hispanic, 2.8 % African-American), premature (20 % <37 week gestational age, 5.7 % <32 weeks gestational age), low birth weight (5.2 % <1,500 g, 13.3 % 1,500–2,499 g), multiple gestation, and born to mothers who had placental problems (placenta previa or preeclampsia) and of older maternal age. Family history of vascular lesions or hemangiomas in first-degree relatives was 32.9 % and 12.3 %, respectively [29]. Chen et al. conducted a study of 650 infants with hemangiomas followed in a Vascular Anomalies Center compared with 650 age-matched controls, and found a slightly increased incidence in females 2:1, twin gestation, <37-week gestational age, birth weight <2,500 g, in addition to maternal first trimester vaginal bleeding, progesterone therapy, and in vitro fertilization, with no substantial differences in older maternal age [30]. Li et al. reported a prospective study of infants in South China over a 3-year period and identified, in addition to multiple gestation, specific risk factors for hemangiomas in their cohort of >1,800 age-matched controls: lower level of maternal education, maternal manual labor, maternal use of medication in the periconceptional period, and family history of hemangiomas [31].

Clinical Features

- **Nearly all lesions visible at the end of the first month**
- **Unique natural history with growth and involution phases**
- **Neither gender nor ethnicity seems to affect the risk of complications**

Course and Presentation

HI are the most common pediatric tumor. Usually absent at birth, or present as a precursor lesion (pink or ecchymotic macules, bruise-like coloring, telangiectatic patch with or without a halo of pallor, or ulceration), virtually all hemangiomas are detectable by the end of the first month of life. Their natural history is strikingly unique with a rapid early proliferative growth phase between 5.5 and 7.5 weeks of age, followed by a late slower growth period (age 6–9 months), and then by a long involuting phase that may last for many years [32]. It is estimated that hemangiomas reach 80 % of their final size by 3 months [33] and growth is completed at a median age of 3 years [34]. Small lesions usually involute with minimal or no scar. If left untreated, larger hemangiomas or those located in special areas such as lips, breast, and nose tip may leave unsightly scarring or even result in permanent disfigurement.

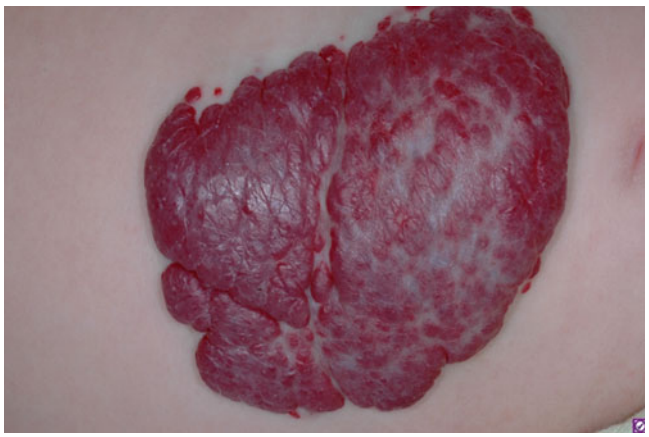

Fig. 26.3 Superficial hemangioma ("strawberry mark")

They may occur anywhere on the skin and mucous surfaces, but there is a clear preference for head, neck, and trunk. Based on their depth, HI can be classified as superficial, deep, and mixed (or combined). Superficial lesions, with proliferating vessels limited to the superficial dermis, are typically bright red and may be present as papule, nodule, or plaque, with a finely lobulated surface, hence the term "strawberry mark" (Fig. 26.3). Deep hemangiomas reach the deep dermis and subcutaneous tissue and present as nodule or tumor with a blue hue, often with a visible venous network. However, in some cases, the overlying skin may show no color changes (Fig. 26.4). Mixed hemangiomas share features of both superficial and deep subtypes (Fig. 26.5).

Morphologically, hemangiomas can be classified as localized, segmental, indeterminate, and multifocal. A localized hemangioma grows from a single focal point (Fig. 26.6). Isolated or grouped hemangiomas along recognizable developmental metameres or with dermatomal distribution are termed segmental (Fig. 26.7). Lesions that cannot be readily identified as either localized or segmental are classified as indeterminate. Multifocal hemangiomas are characterized by ≥8 noncontiguous cutaneous hemangiomas (Fig. 26.8). Hispanic patients are more prone to have segmental hemangiomas [35].

Although the vast majority of HI are represented by solitary lesions, more than one lesion can be detected in up to 30 % of affected infants, and approximately 3 % will develop ≥6 lesions [36]. The amount of cutaneous lesions correlates with the risk of visceral hemangiomas, most frequently hepatic.

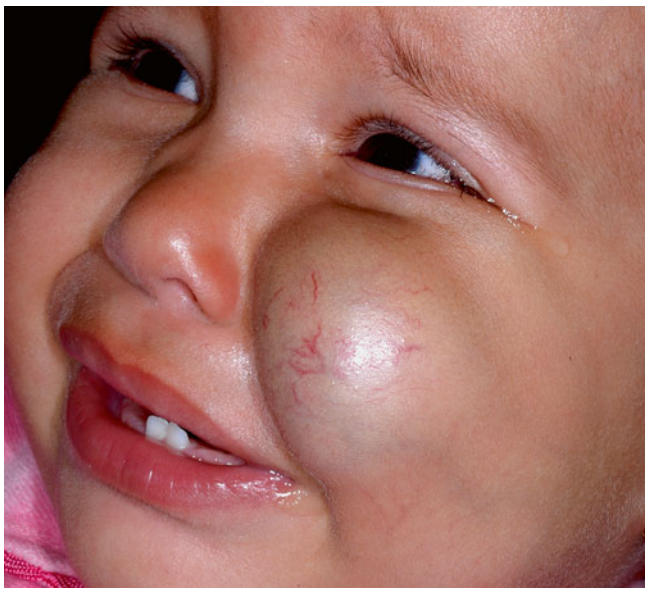

Fig. 26.4 Deep hemangioma. Bluish tumor with overlying telangiectasias

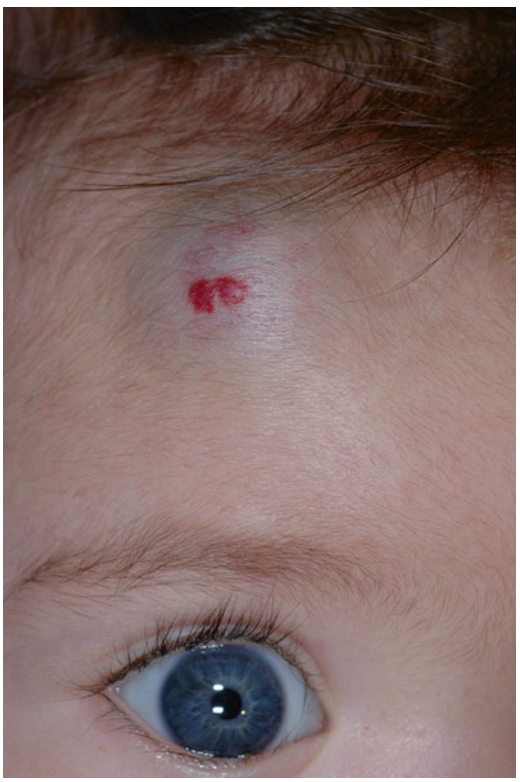

Fig. 26.5 Mixed (compound) hemangioma. Note the bluish hue of the deep component contrasting with the bright red of the superficial portion

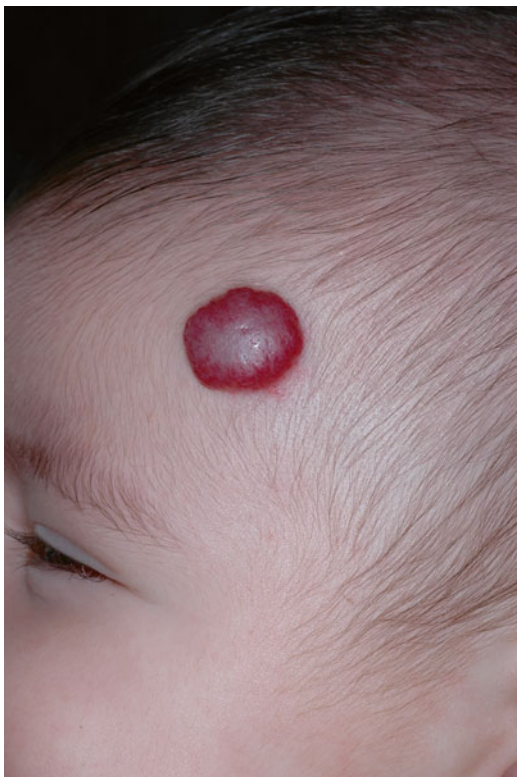

Fig. 26.6 Localized superficial hemangioma

Complications

Although only a minority of patients will experience complications of their HI along its natural history, physicians should to be aware of which circumstances favor the occurrence of such events. Neither sex nor ethnicity seems to play a role in increasing the risk for complications [29].

Ulceration

Ulceration is by far the most common complication and may affect as much as 23 % of patients with HI in a referral setting [37]. The pathogenesis of ulceration is still unclear but is thought to be the result of ischemia and necrosis stemming from trauma and friction, or of the rapid tumor growth exceeding its oxygenated blood supply. Large size and location (lips, diaper area, and neck) are associated with a greater risk of ulceration and propensity for ulceration is much higher in segmental than in localized hemangiomas (33.5 % versus 7.2 %) [36]. Resulting pain can be severe enough to cause sleeping disturbance and feeding difficulties (Fig. 26.9).

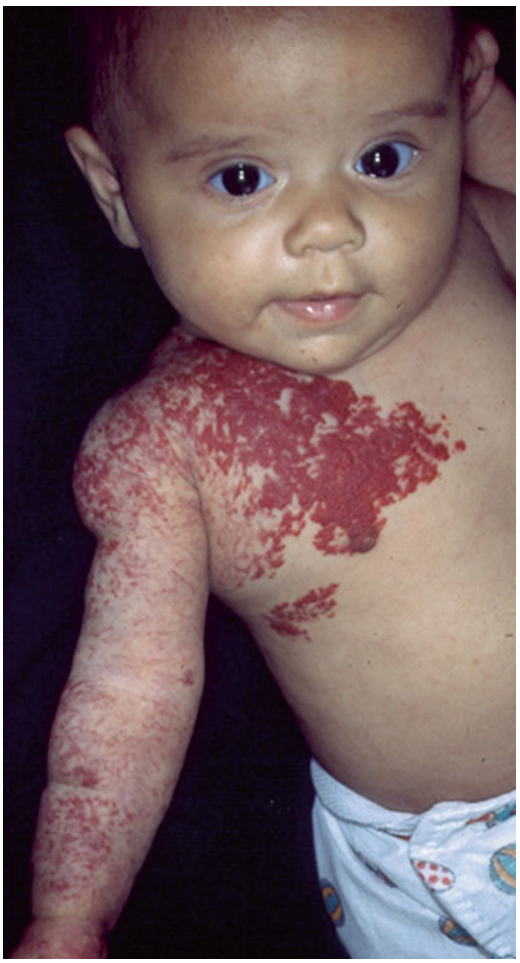

Fig. 26.7 Segmental superficial hemangioma with dermatomal distribution

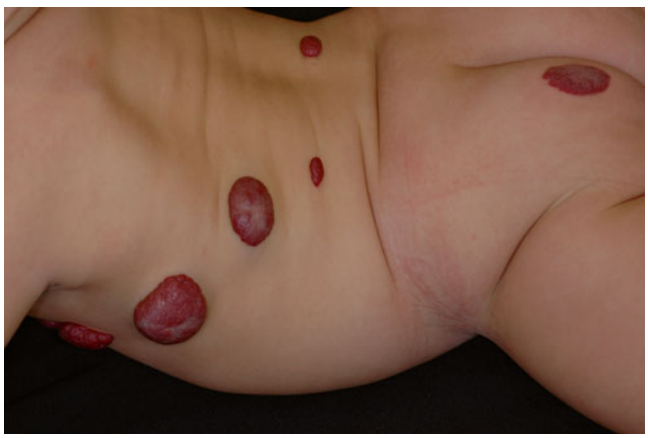

Fig. 26.8 Multifocal superficial hemangioma. This infant had no liver involvement, but presented with congenital agenesia of the left kidney and a cystic lesion in the right kidney

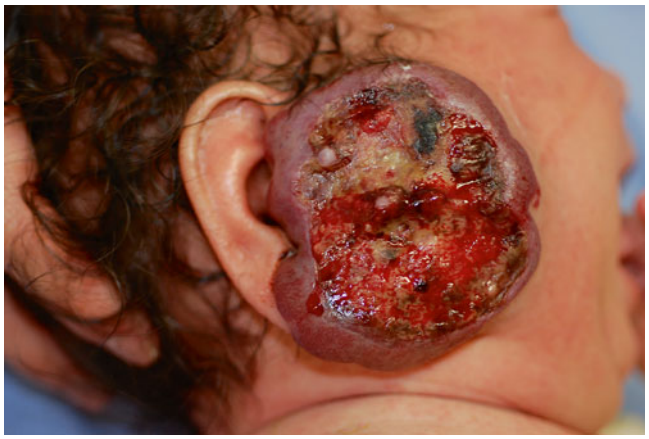

Fig. 26.9 Ulcerated hemangioma of the parotid area

Early white discoloration (average age of 2.6 months) of HI is highly predictive of impending ulceration [38]. This sign should be differentiated from the typically centrifugal discoloration that heralds spontaneous or treatment-induced involution of HI and usually begins after the completion of tumor growth (Fig. 26.10a, b).

Bleeding occurs in 40 % of ulcerations [7]. Life-threatening bleeding is fortunately unusual and may represent a surgical emergency [39].

Visual Impairment

The most common complication of periocular hemangiomas is amblyopia ("lazy eye"), defined as a visual disturbance, without a detectable organic lesion of the eye, arising from inadequate stimulation of the visual cortex of the brain. Refractive errors (astigmatism, myopia), strabismus, or occlusion of the visual axis, by reducing or suppressing the proper image transmission to the brain, are the leading causes of amblyopia and can all be hemangioma induced [40]. The incidence of amblyopia in patients with periocular hemangioma has been reported to be as high as 73 %. However, a recent population-based study has estimated this rate to be 19 % [41].

Concerning the location, periocular hemangioma can be palpebral, extraconal, and/or intraconal. Extraocular muscles (superior, inferior, lateral, and medial rectus) appear in a cone-shaped arrangement in the retrobulbar space (Fig. 26.11). Lesions are considered extraconal or intraconal when located behind the bonny orbit, and outside or inside the muscle cone, respectively. There seems to be a strong association between extraconal and extraconal plus intraconal location and the risk of amblyopia and astigmatism. Palpebral lesions are also able to promote amblyopia and astigmatism in about 30 % of patients [42].

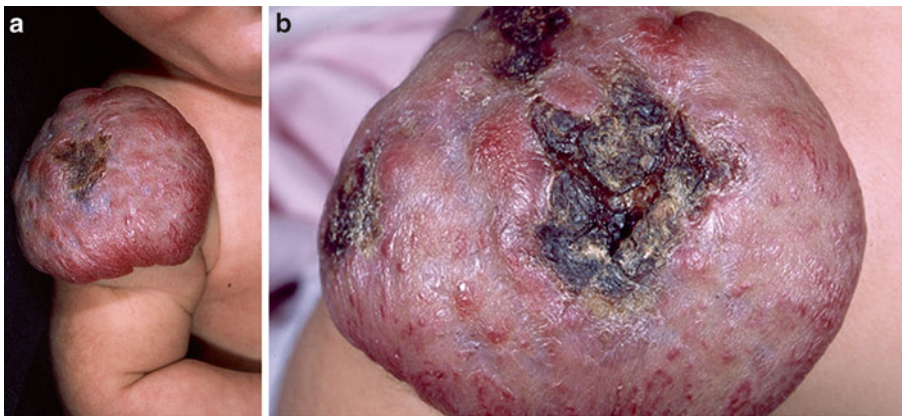

Fig. 26.10 Early discoloration sign. (**a**) Multiple focal whitening areas and imminent ulceration. (**b**) Ulcerations 9 days later

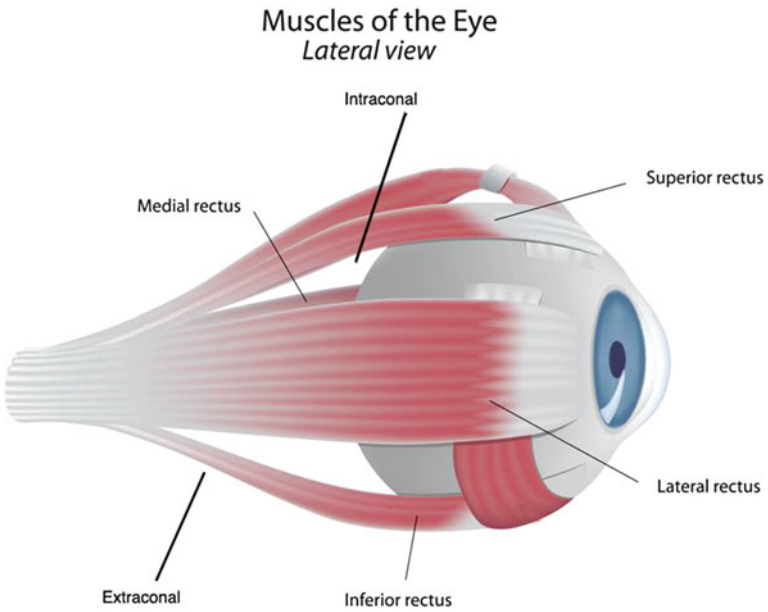

Fig. 26.11 Intraconal and extraconal locations of hemangiomas of the eye

Although small lesions, especially those on the lower eyelid, rarely induce visual dysfunctions, the potential to threaten or permanently compromise vision warrants close and regular ophthalmologic monitoring of virtually all HI of the orbit and eyelids. Imaging (MRI, CT, US) is mandatory to evaluate the tumor size and extension.

Airway Obstruction

Based on the systematic analysis of photographic data, Haggstrom et al. proposed four anatomic patterns (segments S1 to S4) for segmental facial hemangiomas. The frontotemporal S1 segment comprises the lateral forehead, anterior temporal scalp, and lateral frontal scalp. S2 and S3 segments correspond to the maxillary and mandibular prominences, respectively, while the S4 segment encompasses the medial frontal scalp, nasal bridge, nasal tip, ala, and philtrum [36].

The recognition that HI involving the so-called "beard area" (S3 segment-preauricular area, mandible, chin, lower lip, and anterior neck) is a marker for high risk of airway hemangioma is well established in the literature (Fig. 26.12). Bilateral presentation and involvement of multiple regions of the "beard area" increase this risk [43]. However, it should be kept in mind that airway hemangiomas have been demonstrated in association with extrafacial HI [44], with facial HI outside the S3 segment [45], and even in the absence of cutaneous HI.

Hoarse cry, biphasic (inspiration and expiration) stridor, and noisy breathing are classic signs of subglottic hemangiomas. Since many of these lesions are, in practice, accidentally diagnosed during bronchoscopy, respiratory symptoms should prompt otolaryngologic evaluation regardless of the presence of cutaneous HI [45, 46].

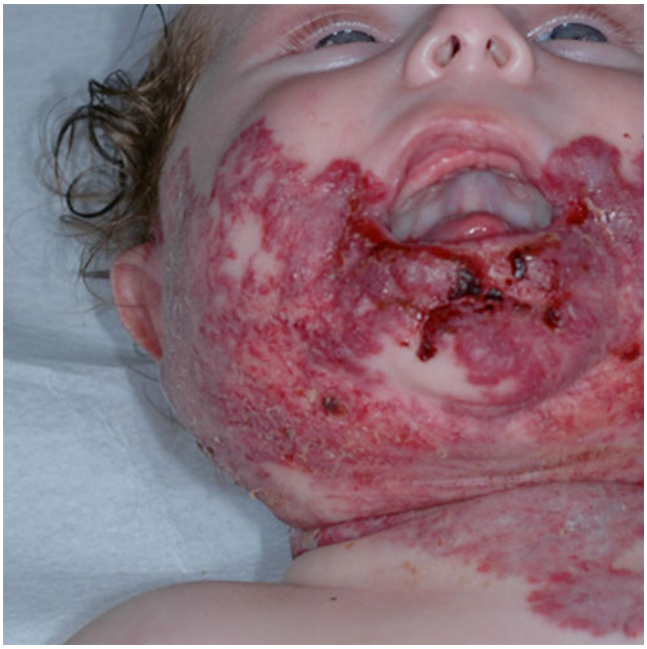

Fig. 26.12 Hemangioma of the "beard area." This infant had no airway hemangioma

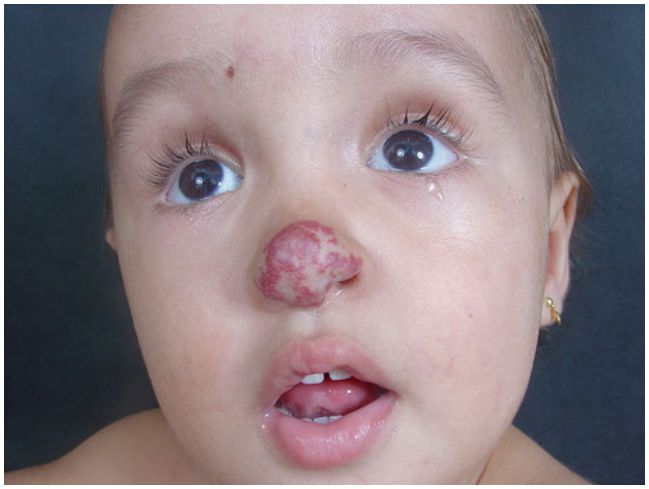

Fig. 26.13 Cyrano's nose: bulging of the tip of nose

Disfigurement

The dogma of the non-interventional approach to HI, which reigned over many decades in the past, was undoubtedly responsible for numerous cases of severe and permanent disfigurement coupled with an enormous impact in these patients' quality of life. Knowledge gathered in recent years, together with the availability of novel therapeutic modalities, allows for the proper management of HI with reduced, or even suppressed, unpleasant aesthetic results. Along with ulceration, prevention of disfigurement is the most common reason for active treatment.

Some anatomic areas are more prone to disfigurement. Ulceration on the lip may result in permanent distortion and lesions on the nasal tip (Cyrano's nose) may cause significant aesthetic impairment (Fig. 26.13). Even small-sized HI, if sessile or pedunculated, can heal with significant fibrofatty residuum (Fig. 26.14a–c). The breast area in girls is another site of concern.

Other Complications

Huang et al. reported a case of severe hypothyroidism in a 3-month-old infant with massive hepatic hemangiomas and high levels of type 3 iodothyronine deiodinase (D3) activity in the hemangioma tissue. This enzyme catalyzes the conversion of thyroxine to reverse triiodothyronine as well as the conversion of triiodothyronine to 3,3′-diiodothyronine, both of which are biologically inactive [47]. The authors postulated that the degradation of the thyroid hormone generated by the intense enzymatic activity of the tumor exceeds the infant's gland capacity to synthesize it.

Subsequently, few cases of HI-induced hypothyroidism have been published. Characteristically, these are associated with large visceral hemangiomas (liver, parotid) [48].

High output cardiac failure is a life-threatening complication generally related to high flow tumors such as hepatic hemangiomas. Approximately 16 % of infants with ≥5 cutaneous hemangiomas have hemangioma of the liver and, hence, routine abdominal US should be performed under these circumstances [49] (Fig. 26.15a–c).

Obstruction of the external auditory canal may lead to otitis and decreased auditory conduction with speech delay.

Associated Structural Abnormalities

The acronym PHACE(s) (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation and other cardiac defects, eye abnormalities, and sternal cleft) describes the association of HI and other anomalies with diagnostic criteria established by consensus [50]. Up to 30 % of patients with large (>5 cm), facial segmental hemangiomas will present PHACE(s) syndrome. Although the risk is higher for lesions located along frontotemporal (S1) or mandibular (S3) areas, any segment may be involved [51]. Hispanic infants are more likely to have their segmental hemangiomas associated with PHACE(s) syndrome [35]. On the other hand, hemangioma distribution does not predict the occurrence of cardiovascular anomalies [52].

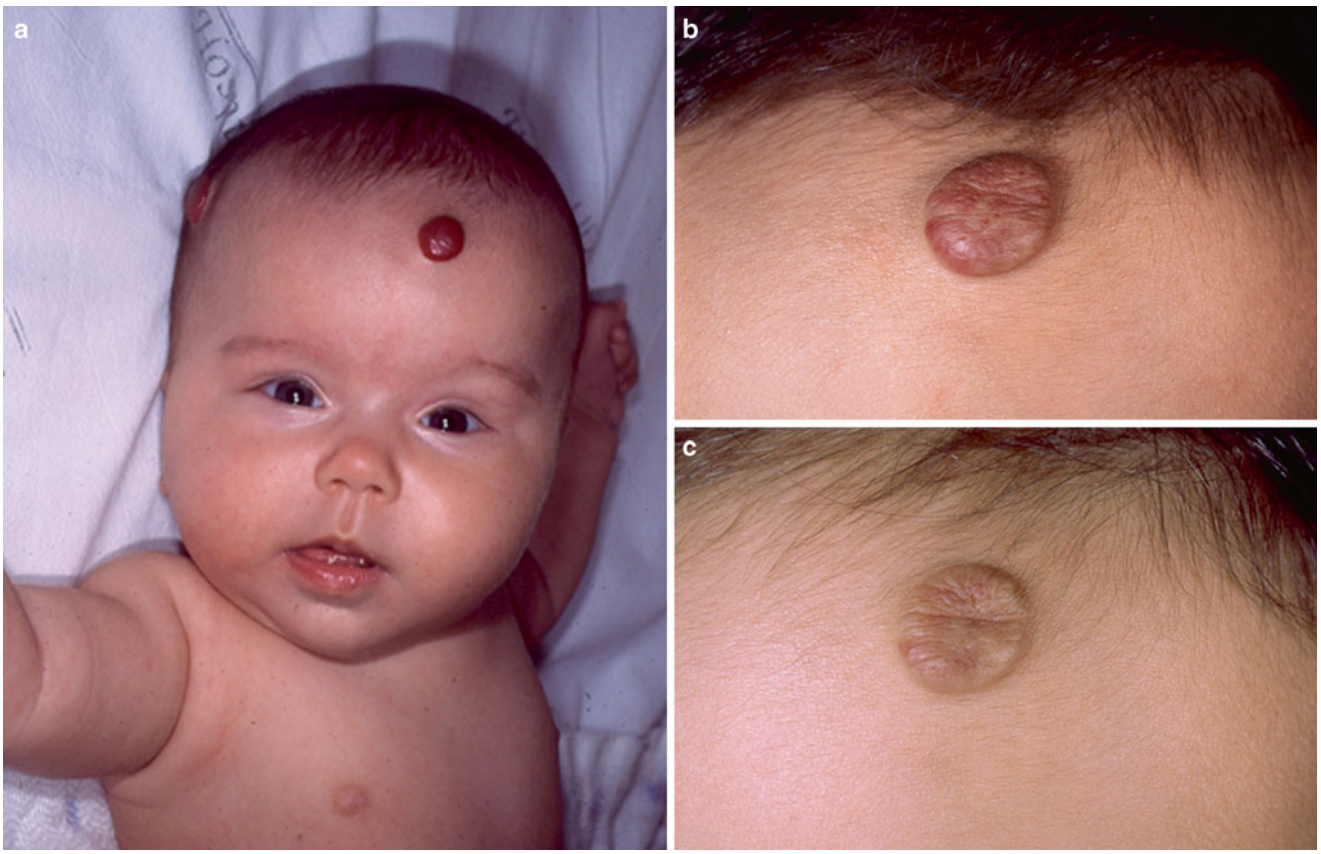

Fig. 26.14 Spontaneous resolution of hemangioma. (**a**) At age 3 months. (**b**) Flattening and discoloration at age 2 years. (**c**) Fibrofatty residuum at age 3 years

LUMBAR (lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies), PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag syndrome), and SACRAL (spinal dysraphism, anogenital, cutaneous, renal, and urological anomalies, associated with an angioma of lumbosacral localization) are acronyms that refer to the association of large segmental HI of the lumbosacral or perineal areas and underlying structural abnormalities.

Treatment

- **Timely referral is essential, as early treatment can prevent unwanted morbidities.**
- **Treatment options may vary based on timing of treatment onset, location, and type of hemangioma**
- **Combined therapies may be preferable.**

Considering typical hemangiomas of infancy, timely referral is indispensable to determine whether further evaluation or treatment is warranted. Age of the patient, hemangioma location, its morphology, size, the number of lesions, associated (or impending) symptoms, and/or structural anomalies contribute to management decisions. Proactive early therapy can prevent the need for more invasive interventions and/or surgery in the future.

Laser Treatment

Early pulsed dye laser may be beneficial in preventing proliferation in early superficial hemangiomas, whereas pulsed dye or other lasers may ameliorate residual telangiectasias or contour irregularities after involution [53–56]. Regarding laser treatment, skin of color is pertinent to the treatment of vascular anomalies. Chaplin and Jablonski note that "melanin accounts for most of the variation in the visual appearance of human skin," demonstrating that skin color correlates with environmental UV radiation, and variations in human

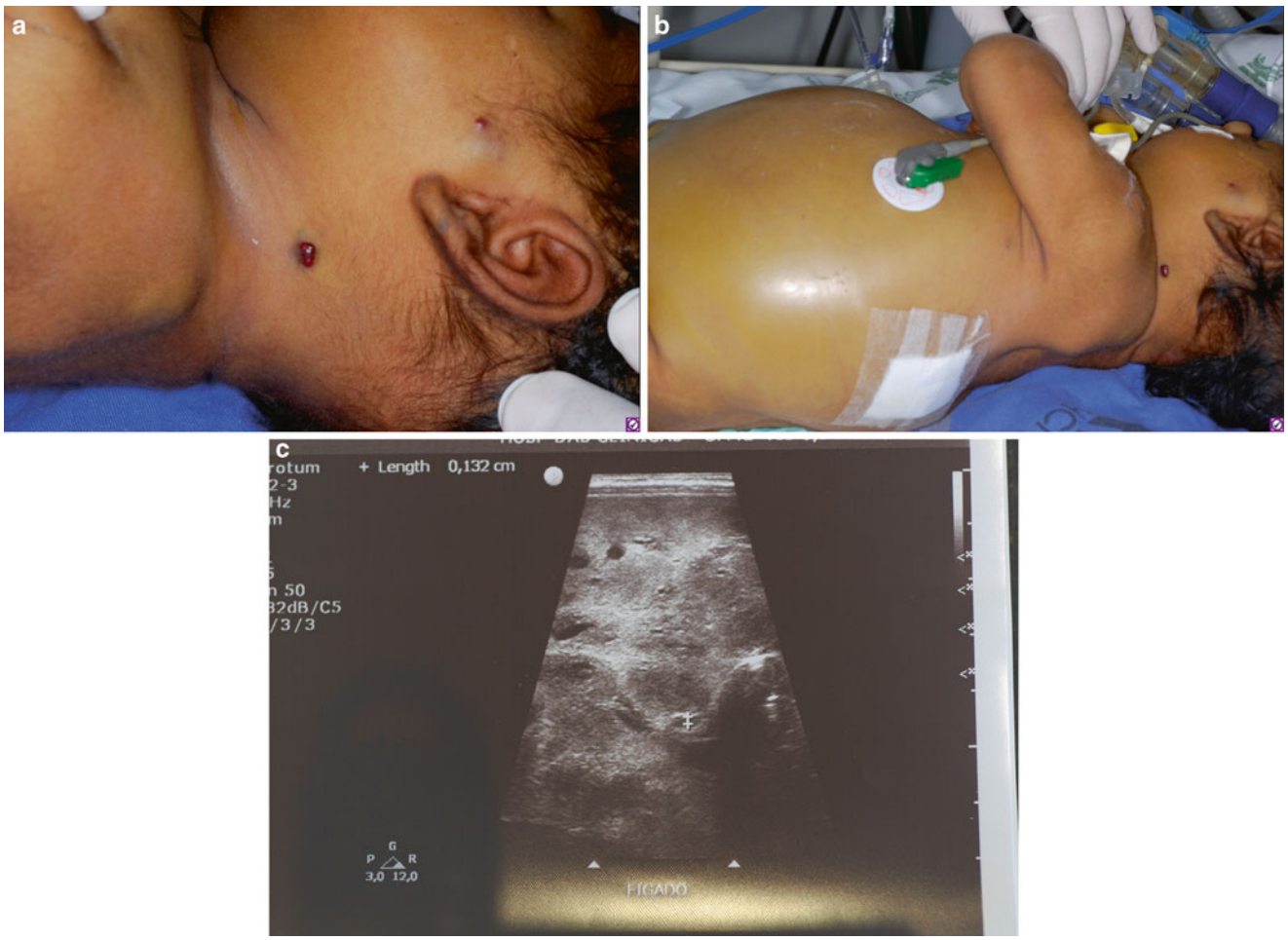

Fig. 26.15 Multifocal hemangioma with fatal outcome. This patient had 11 small-sized GLUT1 positive lesions. (**a**) Hemangiomas on the face, neck, and earlobe. (**b**) Abdominal distension secondary to massive liver invasion. (**c**) US showing diffuse liver hemangiomas

melanin pigmentation are adaptive to ameliorate the consequences of UV radiation (damage to dermal blood vessels, sweat glands, etc.). They further posit "skin reflectance, particularly in the wavelength approximating the absorption maximum of oxyhemoglobin (545 nm), has been optimized by natural selection to balance the conflicting requirements of prevention of folate photolysis (photoprotection) and previtamin D3 synthesis (requiring UV penetration)" [57, 58]. Dark (melanized) skin (as seen in equatorial and tropical climates) provides photoprotection and abrogates UV-damage-related interference with thermoregulation. Conversely, fair-skinned individuals (in the northernmost locations) require UV exposure for D3 synthesis. These findings are anthropologically interesting, and relevant to the current laser therapies of vascular lesions.

Various laser treatments for vascular anomalies (pulsed dye, Q-switched ruby, Q-switched neodymium:yttrium-aluminum-garnet (Nd:YAG), Q-switched alexandrite, intense pulsed light, intralesional photocoagulation (ILP), fractional CO_2, and potassium-titanyl-phosphate (KTP) 1,064-nm lasers) have been used, tailored to the type and location of vascular lesion, age of the patient, and desired outcome [54, 59–62]. Pulsed dye laser therapy, which is typically used for hemangiomas and capillary malformations, is delivered at a wavelength of 595 nm in the green-yellow spectrum and is customary for cutaneous vascular lesions (hemangiomas, telangiectasias, capillary malformations) (Fig. 26.16).

At this wavelength, the laser is preferentially absorbed by the chromophore oxyhemoglobin in red blood cells, causing selective photothermolysis in blood vessels and vessel clearing [63, 64]. Notably, epidermal melanin absorbs the same wavelength as oxyhemoglobin, hampering pulsed dye laser absorption in the blood vessels and rendering laser treatment less effective (Fig. 26.17).

To minimize undesirable pigmentary changes, laser therapy in populations with dark skin (e.g., African, Asian) requires dynamic cooling techniques (now standard on pulsed dye laser equipment) and parameter adjustments [66–71]. Preliminary studies suggest laser-induced changes in angiogenesis-related gene expression [72], and superior

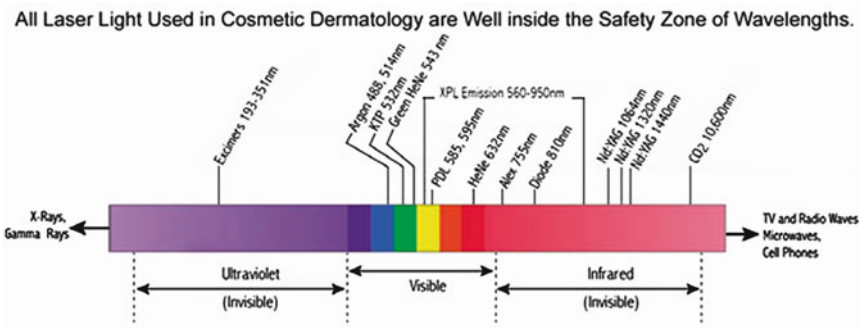

Fig. 26.16 Relative positions of various types of lasers on the electromagnetic spectrum. http://www.shinobayderm.com/laser_tech.html

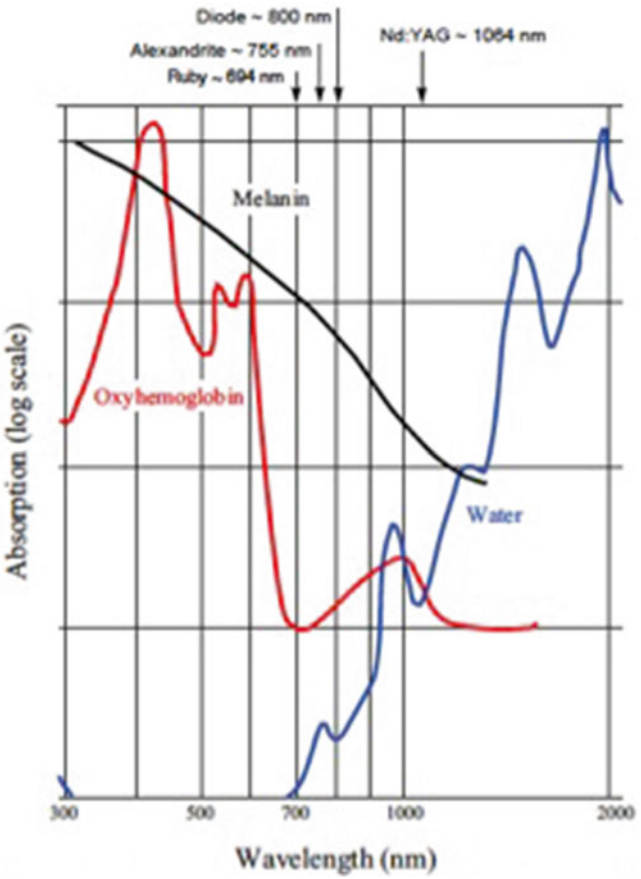

Fig. 26.17 The absorption of various chromophores as a function of wavelength (adapted from [65], #4331). www.aesthetic.lumenis.com/pdf/laser_principles_aspects.pdf

vessel clearing by combination therapies with laser and topical agents (e.g., imiquimod, rapamycin) may correlate with extended post-laser anti-antiangiogenic local effects of these drugs [73–75].

Medical Therapy

Medical therapy for hemangiomas has been historically delivered topically, intralesionally, and/or systemically. Until Léauté-Labrèze's publication in 2008, documenting the serendipitous observation of the effectiveness of beta-blockers for hemangiomas, systemic, topical, or oral corticosteroids were first-line therapy for proliferating hemangiomas requiring medical treatment [76]. Since then, over 350 manuscripts regarding Propranolol and hemangiomas have been published, describing clinical efficacy (in the majority of studies) for hemangiomas of varying types: ulcerated, periocular, airway, segmental (including PHACE), and hepatic hemangiomas, with no reported ethnic difference in response [77–88]. Potential adverse side effects of Propranolol include cool extremities, gastrointestinal symptoms, hypotension, nocturnal restlessness, reactive airways, and bradycardia with rare but significant reports of hypoglycemia [81, 87, 89–94]. The precise mechanism of action of Propranolol is not known; however, several studies demonstrating its molecular effects are summarized in Table 26.3. Clinical studies using selective beta-blockers (potentially having fewer short- and long-term side effects) are ongoing [95–97]. Combination therapy with laser and Propranolol is promising [98–100].

Topical beta-blockers may be effective for focal, superficial, deep, and/or ulcerated hemangiomas [101–106]. Intralesional propranolol was described as successful in one study; however, it was not recommended in two subsequent reports [107–109]. The use of steroids or surgery as frontline therapy for hemangiomas is less commonly reported [110–113].

Surgery

Early surgical removal of hemangiomas may be warranted if symptoms are not manageable by other means (e.g., bleeding, amblyopia, astigmatism) or in specific anatomic locations (e.g., early excision of large scalp hemangiomas benefit due to greater laxity of the infant scalp) [129]. Later surgery is often necessary due to unsatisfactory aesthetic results (e.g., tissue redundancy, scarring, anatomic deformity) after involution. Postsurgery keloid scar formation occurs with a higher incidence in pigmented skin in patients of African, Asian (especially Chinese), and Hispanic descent [130].

Table 26.3 Propranolol proposed mechanisms of action

Proposed mechanism of action	Reference
Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells G/G phase cell cycle arrest, inhibition of VEGF-induced tyrosine phosphorylation of VEGF-R-2, in vitro inhibition of chemotactic motility and differentiation of endothelial cells, matrix metalloproteinase inhibition	[114]
Early vasoconstriction (decreased nitrous oxide) Angiogenesis inhibition (interference with VEGF- and bFGF-induced endothelial cell proliferation) Apoptosis induction	[3]
Inhibition of angiotensin-converting enzyme and angiotensin II receptor 2, resulting in decreased ATII and VEGF	[115]
Hastens adipogenesis in hemangioma stem cells Activates apoptosis of hemangioma endothelial cells	[116]
Endothelial cell type independent Blockade of endothelial cell proliferation, migration, VEGFR-2, and interferes with multiple proteins modulating endothelial and hemangioma endothelial function	[117]
Inhibition of hemangioma endothelial cell proliferation and induction of apoptosis, dose-dependent vascular endothelial growth factor (VEGF) expression downregulation	[118]
Inhibition of hemangioma β2-adrenoceptors	[119]
Inhibition of hemangioma endothelial nitric oxide synthase (eNOS) protein	[120]
Hypoxia-inducible factor (HIF-1alpha)-related inhibition of VEGF-A-mediated angiogenesis, via PI3/Akt and p38/MAPK pathways	[121]
Targeting hemangioma endothelial cell pericytes (?)	[122]
Decreased serum VEGF level in propranolol-treated hemangioma patients within first month of treatment	[123]
G0/G1 phase cell cycle arrest of hemangioma endothelial cell proliferation ?ERK signaling downregulation, interference with VEGF-R-mediated hemangioma endothelial proliferation	[124]
Hemangioma-derived endothelial cell apoptosis, decreased VEGF expression	[125]
Inhibition of endothelial progenitor cell homing	[124, 126]
Apoptosis induction via activation of the intrinsic and extrinsic apoptotic pathways	[124, 127]
Growth inhibition, not apoptosis of hemangioma cells	[128]

Ongoing Research

"Typical" hemangiomas of infancy undergo an early proliferative angiogenic phase followed by a gradual involution phase characterized by apoptosis and adipogenesis (i.e., fibrofatty tissue replaces vascularity) [131]. One theory proposes that a fetal placental progenitor is the originator of infantile hemangiomas [132]. Estrogen receptors have been detected in hemangioma tissue, and elevated endothelial growth factor and estrogen levels have been detected in patients with hemangiomas [133]. Various cell types are present in hemangiomas: endothelial cells, pericytes, macrophages, mast cells, mesenchymal stem cells, and adipocytes. Hemangioma endothelial cells have been noted to be clonal, and specific signaling pathways have been identified [134–136]. Ongoing studies are ascertaining mechanisms of action of current therapies and will ideally identify innovative pharmacologic approaches [137, 138].

Summary/Conclusion

Hemangiomas of infancy represent a relatively common disorder, with a unique natural history. Although the cellular features are benign, it is essential to identify potential risk factors, which may be associated with significant morbidity. The incidence of hemangiomas is less frequent in skin of color. There does not appear to be a difference in clinical behavior in different ethnic groups; however, further studies are warranted to assess this more critically.

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Congenital Melanocytic Nevi

27

María del Carmen Boente

Abstract

Pigmentary nevi are the most common skin neoplasm found in humans with an incidence of 3 % in whites and 16 % in black infants at birth. The incidence of melanocytic nevi increases throughout infancy and adulthood, as well as at puberty, during pregnancy and with hormonal therapy. Congenital melanocytic nevi (CMN) are defined as neural crest derived benign nevomelanocytic proliferations that are present at birth or in the few weeks of life. They are genetically determined and persist throughout life. Prevalence of CMN is 1–2.4 % of newborns; African and Japanese decent have higher incidence than Hispanics or whites and the incidence is 1:500,000. Prevalence of CMN is 1–2.4 % of newborns; African and Japanese decent have a higher incidence than Hispanics or whites and the incidence is 1:500,000. A new classification for determining risks of adverse events in CMN includes the following criteria: satellite nevus count, anatomic localization, color heterogeneity, surface, rugosity, hypertrichosis, and dermal or subcutaneous nodules. They are more frequent on the trunk and extremities, brown-black in color, with small nodules and coarse hair, with a regular smooth and well demarcated border. Satellite melanocytic nevi are common. Proliferative nodules may appear within the nevus, which usually represent benign neurotization of the lesion.

By dermatoscopy, the main pattern seen in congenital nevi is the so-called cobblestone pattern, constituted of large, angulated globules, resembling cobblestones. Excision of CMN before the development of malignant melanoma (MM) should be considered to reduce the chances of malignant melanoma development and cosmetic reasons, although it is technically difficult, and complete removal is often impossible.

Keywords

Nevi • Melanocytes • Congenital melanocytic nevus • Small congenital melanocytic nevus • Medium congenital melanocytic nevus • Large congenital melanocytic nevus

Introduction

A nevi can be defined as a "visible", circumscribed, long-lasting lesion of the skin or the neighboring mucosa, reflecting genetic mosaicism. Pigmentary nevi are the most common skin neoplasm found in humans with an incidence of 3 % in whites and 16 % in black infants at birth. Of 1,058 newborns younger than 72 h of age, 4 % were noted to have pigmented lesions; of these, only one-third have melanocytic nevi by cutaneous biopsy. The incidence of melanocytic nevi increases throughout infancy and adulthood. They also increase in size and pigmentation at puberty, during pregnancy and with hormonal therapy [1–3]. Among these, congenital melanocytic nevi (CMN) are defined as neural crest derived benign nevomelanocytic proliferations that are present at birth or in the few

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Table 27.1 Classification for CMN from Hamm and Höger [9]

Description	Size (cm)[a]	Incidence
Small	<1.5	Roughly 1:100
Medium	1.5–19.9	Roughly 1:1,000
Large	≥20	Roughly 1:20,000
Giant	>40–50	Roughly 1:500,000

[a]Relates to the largest diameter that is reached in adulthood. The largest diameter of CMN increases between birth and adulthood by a factor of 1.7 on the head, 3.3 on the legs, and 2.8 on the trunk, arms, and feet

weeks of life. They are genetically determined and persist throughout life [4–6]. Somatic mosaicism for genes likely to be lethal in the germline has been proven to be the cause of several mosaic phenotypes. Kinsler et al. [7] provide evidence that such a hypothesis is also true for CMN [7, 8].

Because the size of CMN increases during childhood in proportion to the growth, CMN are classified by the largest diameter that they are likely to reach in adulthood (projected adult size [PAS]) (Table 27.1) [9–13]. There is no general consensus on this classification. Krengel el al. [6] postulate that from birth to adulthood, the area of the head grows by a factor of 2.8, trunk and arms by a factor of 8, and legs by a factor of 12. With this criterion they are subdivided into three groups based on their size: small (<1.5 cm), medium (1.5–20 cm), and large or giant (>20 cm) in their projected adult size. Such a classification is important due to the higher incidence of melanoma in the larger sized CMN, as well as, of neurocutaneous melanosis, greater cosmetic impairment, higher complexity of surgical removal, and higher risk of extracutaneous malformations in this group [6, 9, 10, 14].

Besides CMN diameter Krengel et al. [12] proposed a new classification for determining risks of adverse events that includes the following criteria: satellite nevus count, anatomic localization, color heterogeneity, surface, rugosity, hypertrichosis, and dermal or subcutaneous nodules (Table 27.2). Future development of a molecular genetic-based classification may greatly benefit from correlation with a standardized morphologic classification of CMN.

Epidemiology/Demographics

- Prevalence of CMN is 1–2.4 % of newborns
- Race: African and Japanese decent higher incidence than Hispanics or whites
- Incidence of giant CMN: 1:500,000

CMN are common neoplasm of the newborn skin; the estimated prevalence of CMN varies widely depending on the study, ranging from 0.5 to 31.7 %. GCMN are uncommon among them [3, 5, 15–18]. Most of them are 3–4 cm in diameter; the incidence of lesions greater than 10 cm in diameter has been calculated as only 1 in 20,000 newborn. Larger ones are less common. GCMN have an estimated incidence of 1 in 500,000 live births (Table 27.1) [4, 9, 14]. Kanada et al. [19] in a prospective study enrolled 594 infants in San Diego, California, USA, seen in the first 48 h of life, to provide data based on ethnicity, prematurity, and body site for vascular, pigmented, and other common cutaneous findings and compared their results with previous international prospective studies. In their study CMN was defined as flat or raised, tan brown or black, usually sharp regular symmetrical borders. CMN were found in 2.4 % of the studied newborns, among them 2.6 % were Caucasian, 17.9 % were African-American, 1.9 % Asian, none lesions were found among Hispanic patients, and 1.3 among other races (Table 27.3). Comparing their study with the incidence of CMN in previous international studies is shown in Table 27.4. Using the sliding scale metric defined by Marghoob et al. [10] for infants, all CMN reported in Kanada et al. [19] study qualified as small or medium. No neonate has more than one CMN, and none had large or giant CMN. People of African and Japanese decent appear to have higher incidences of CMN than Hispanics or whites [15–18, 20–28].

Although patients with darker skin types usually develop malignant melanoma (MM) in nonglabrous skin, as in patients with lighter skin types, there are multiple reports of MM associated with GCMN in patients with darker skin [4, 17].

Clinical Presentation

- Localization: more frequent on the trunk and extremities, but head and neck lesions more disfiguring.
- Classical presentation: brown-black elevated plaque studded with small nodules and coarse hair, with a regular smooth and well demarcated border. Satellite melanocytic nevi common among GCMN.
- Lesions usually increase in size, color, and more hair, but pigmentary regression can occur.
- Proliferative nodules may appear within the nevus, which usually represent benign neurotization of the nevus

The classical presentation of CMN is a brown-black elevated plaque studded with small nodules and coarse hair, with a regular smooth and well demarcated border [5, 29, 30]. Compared to benign acquired nevi, CMN are larger in size and display a mottled heterogeneous morphology (Fig. 27.1). They typically occur on trunk (38 %) and extremities (38 %). Head and neck lesions are infrequent (14 %) but quite disfiguring [4–7, 31]. The clinical appearance may change with age. In neonates, they may be lighter in color and relatively hairless, with flat poorly marginated border, or raised darkly pigmented, well marginated lesion with an irregular rugged surface, associated with dense, coarse, darkly pigmented hairs. In childhood, there is a progressive darkening of lightly colored lesions, and may acquire long, coarse, darkly pigmented

Table 27.2 Proposed classification of CMN by Krengel et al.

CMN parameter	Terminology	Definition
CMN projected adult size	Small	<1.5 cm
	Medium	
	M1	1.5–10 cm
	M2	10–20 cm
	Large	
	L1	>20–30 cm
	L2	>30–40 cm
	Giant	
	G1	>40–60 cm
	G2	>60 cm
	Multiple medium size	≥3 medium CMN without a single predominant CMN
CMN localization[a]		
Head	Face, scalp	
Trunk	Neck, shoulder, upper back, middle back, lower back, breast/check, abdomen, flank, gluteal region, genital region	
Extremities	Upper arm, forearm, hand, thigh, lower leg, foot	
No. of satellite nevi[b]	S0	No satellites
	S1	<20 satellites
	S2	20–50 satellites
	S3	>50 satellites
Additional morphologic characteristics	C0, C1, C2	None, moderate, marked color heterogeneity
	R0, R1, R2	None, moderate, marked surface rugosity
	N0, N1, N2	None, scattered, extensive dermal or subcutaneous nodules
	H0, H1, H2	None, notable, marked hairiness

CMN congenital melanocytic nevi
[a]One or more locations should be used to described preponderant area of involvement
[b]Refers to number of satellites within the first year of life. In case of data not available, actual number should be used

Table 27.3 Incidence of CMN. From Kanada et al. [19]

Cutaneous lesion	Total (%)	Caucasian (%)	Hispanic (%)	African-American (%)	Asian (%)	Other (%)
CMN	2.4	2.6	0	17.9	1.9	1.3
Small	1.3	1.5	0	10.7	0	1.3
Medium	1	1.1	0	7.1	1.9	0
Large/giant	0	0	0	0	0	0

Table 27.4 Incidence of CMN in International Studies. Modified from Kanada et al. [19]

	Kanada et al.	Alper and Holmes	Jacobs and Walton	Shih et al.	Magaña-García and Gonzales-Campos	Kahana et al.	Tsai and Tsai	Karvonen et al.	Nanda et al.	Hidano et al.	Dickson and Yue
Country	US	USA	USA	Taiwan	Mexico	Israel	China	Finland	India	Japan	Australia
Year publication	2011	1983	1976	2007	1997	1995	1993	1992	1989	1986	1979
Number of patients	594	4,641	1,058	500	1,000	1,672	3,345	4,346	900	5,387	100
CMN (%)	2.4	1.1	1.0	0.6	2.5	0.35	1.0	1.5	0.44	2.7	1.0

terminal hairs in 75 % of them. Less commonly lanugo hairs overlie the lesion (Figs. 27.2 and 27.3) [4, 5, 30].

The color is generally uniform, but sometimes they exhibit considerably pigment color variation. Nearly all CMN have brown as their primary color, although it may be admixed with black, blue, and gray (Fig. 27.4). With the passage of time CMN may get darker, lighter, loose pigmentation, become more heterogeneous, or, rarely, regress (Fig. 27.5) [4, 11, 31].

The surface of CMN may be smooth, but frequently as the patient ages, a papular, pebbly, verrucous, or even cerebriform appearance became evident. Proliferative nodules may

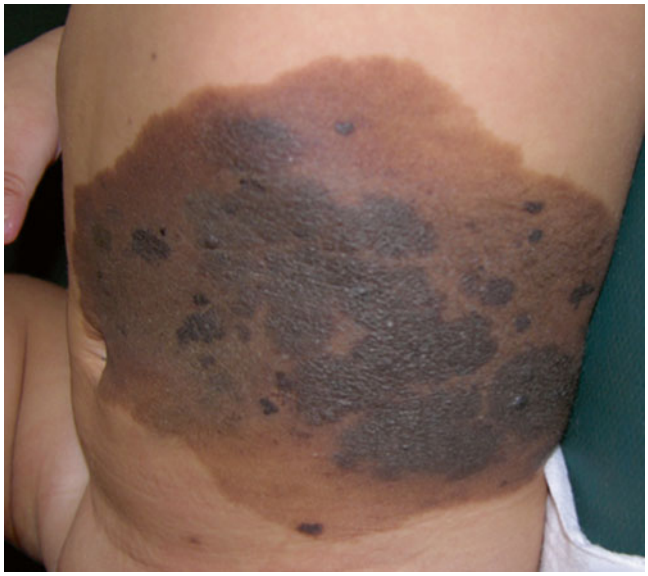

Fig. 27.1 Large CMN: Note different colors and surface changes within the nevus. Several "proliferative nodules" are present

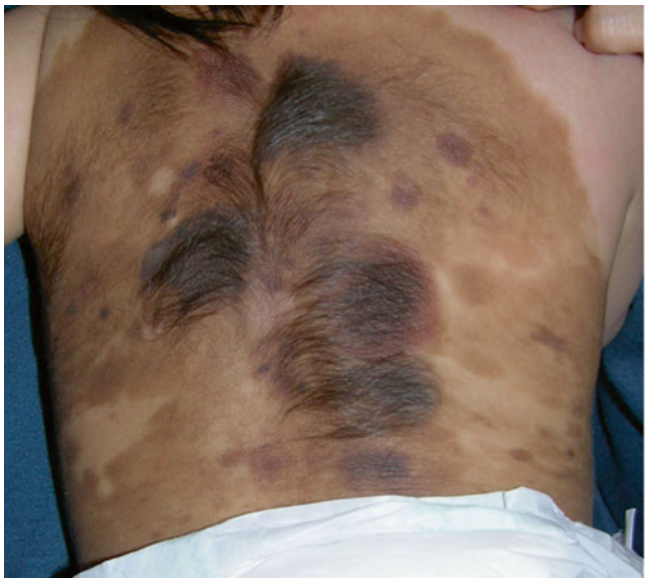

Fig. 27.2 GCMN: Note heterogeneous colors and morphology. Coarse terminal darker pigmented hair is noted in some areas of the nevus

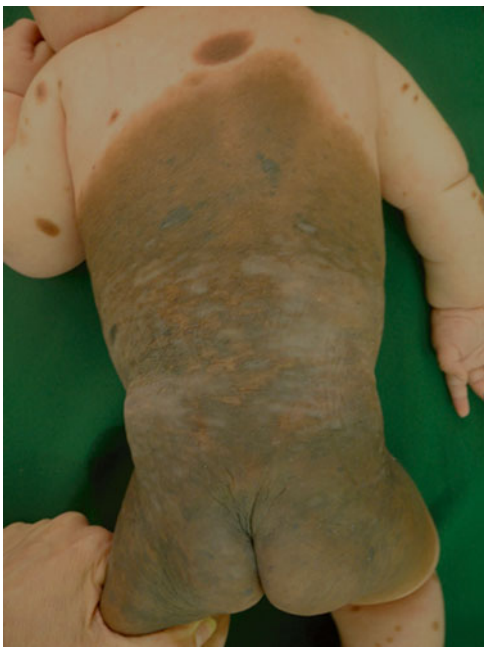

Fig. 27.3 Giant CMN on the trunk and proximal inferior limbs; Note different colors and structures. "Proliferative nodules" are also observed. Note satellite lesions

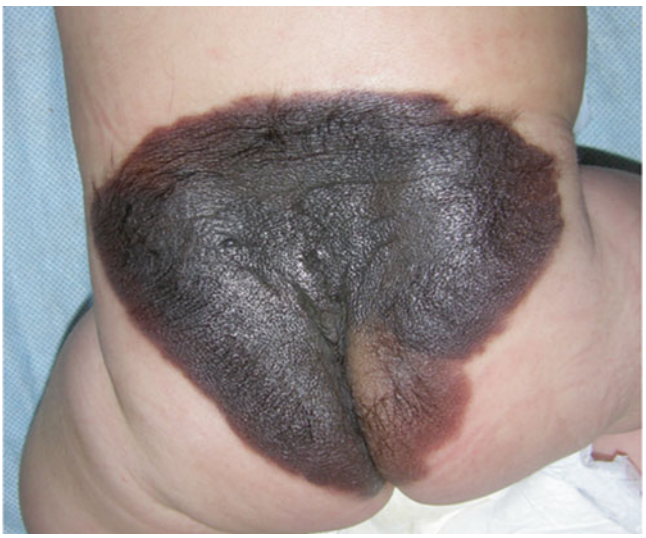

Fig. 27.4 Large CMN. Note more homogeneous dark brown color and vellus, lanugo hairs cover most of the nevus surface

appear within the nevus, which usually represent benign neurotization of the nevus [4–6, 11, 32].

GCMN are often associated with satellite melanocytic nevi; these are smaller CMN that are present at birth or arise months to years later (Fig. 27.6) [11, 32].

CMN have a dynamic course and may change over time. They can increase in size during childhood, become darker in color, become hairy, or show pigmentary regression. Spontaneous involution of CMN is rare and is usually associated with hypopigmented halo phenomenon or vitiligo (Fig. 27.7) [33–35]. Cusack et al. [36] described a case of complete regression over a 4-month period with the halo phenomenon of a medium-sized CMN. A control biopsy showed prominent lymphocytic infiltrate in the papillary dermis and aggregates of lymphocytes adjacent to the nevus in the deeper dermis, supporting an autoimmune mediated phenomenon which involves T-cell immunity and the presence of IgM autoantibodies [37, 38].

Spontaneous regression without the halo phenomenon has also been described. Despite the clinical involution,

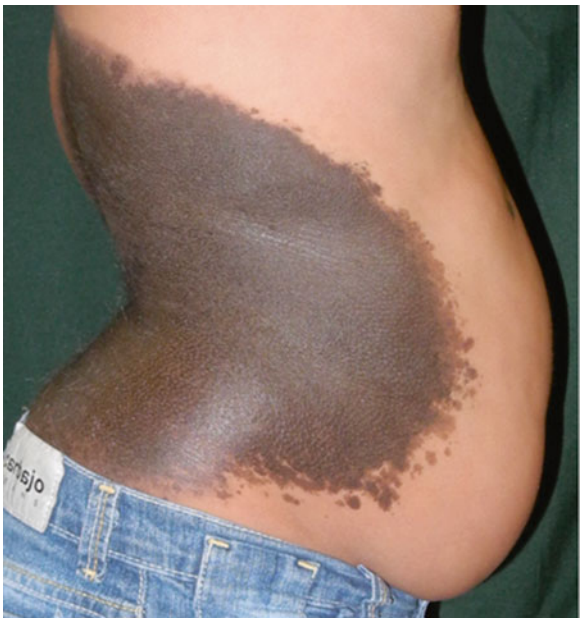

Fig. 27.5 GCMN on the trunk. Note uniform color and lanugo-like hairs

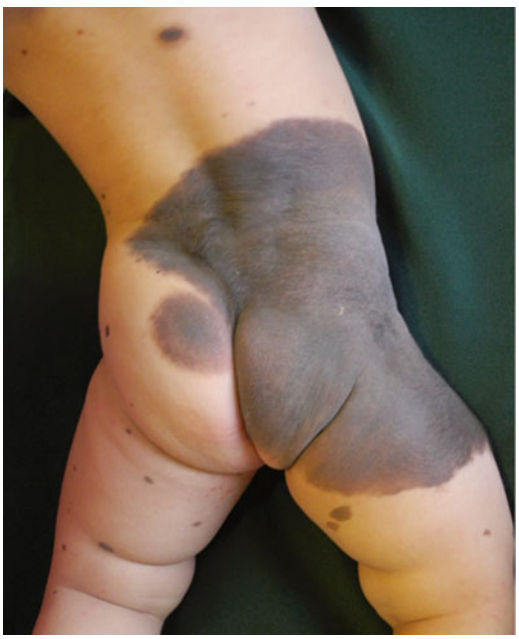

Fig. 27.6 Giant congenital bathing suit type nevus. Note smaller "satellite" lesions

pigment regression may be accompanied by histological persistence of nevus cells. Halo nevi usually occur during childhood or adolescence [3]. The depigmentation may occur within the lesion, around it or at a distant site (Fig. 27.8a–d) [37]. Spontaneous regression of a CMN starts with loss of terminal hairs and epidermal pigments resulting in bluish color of the plaque, which is followed by flattening and loss of dermal pigments resulting in vitiligo-like leukoderma. Dermal nevus cells, however, do not disappear; they just loose the ability to produce melanin pigments. The process of regression is associated with lymphocytic infiltration [37].

Regression of CMN without the halo phenomenon has been described [33]. Vilarrasa et al. [39] reported the clinical cases of medium-to-large CMN that clinically disappeared without the halo phenomenon. In both cases, skin biopsies showed that a high proportion of amelanotic nevus cells were still present in the dermis and even extended to the subcutaneous fat and pilosebaceous unit, indicating a decrease in melanin production by dermal nevus cells, rather than a reduction in their number [11, 33, 40–43].

Desmoplastic hairless hypopigmented nevus (DHHN) was first described by Ruiz-Maldonado et al. [44] as a hard, ligneous, progressively hypopigmented and alopecic GCMN. In such cases they noted progression of the induration in three cases and regression in the other patient. Histopathological (HP) appearance is characterized by intense dermal fibrosis and nevus cell depletion without evidence of malignant transformation. Boente and Asial [45] described a case of DHHN in which a well demarcated tumor appeared during the follow-up. Histology of such tumor showed nevus cells of normal morphology between thick collagen bundles; immunostaining revealed that such nevus cells have S100+, Vim+, HMB45 staining. An immune response against the melanocyte of the nevus may explain this type of evolution. Persistence of nevus cells was described in a case of involution of a neonatal eroded giant CMN with desmoplastic reaction (Fig. 27.9a–c) [46].

CMN rarely affect the scalp in the form of a giant cerebriform nevus; the skin is thrown into folds resembling the undulation of the cortical surface of the brain [30].

Kissing nevus or divided nevus of the eyelid occurs in adjacent parts of the upper and lower eyelids. When the eyelid is closed it appears as a single lesion. This implies that CMN develop between the 9th and 20th week of gestation, when the eyelids are fused (Fig. 27.10) [5, 47].

Histopathological Features

Tannous et al. [5] emphasized some distinctive HP features to suspect a congenital onset: (1) the presence of nevomelanocytes within the lower two-thirds of the dermis and within the subcutaneous tissue; (2) nevomelanocytes splaying or extending between the collagen bundles of the reticular dermis as single cells, "Indian" files, or cords of cells; (3) extension of nevomelanocytes around and within hair follicles, sebaceous glands, eccrine apparatus, vessel walls, and nerves; (4) a perivascular and perifollicular distribution of nevomelanocytes simulating an inflammatory reaction such as figurate erythema; and (5) arrector pili that may be enlarged, distorted, and infiltrated by nevomelanocytes.

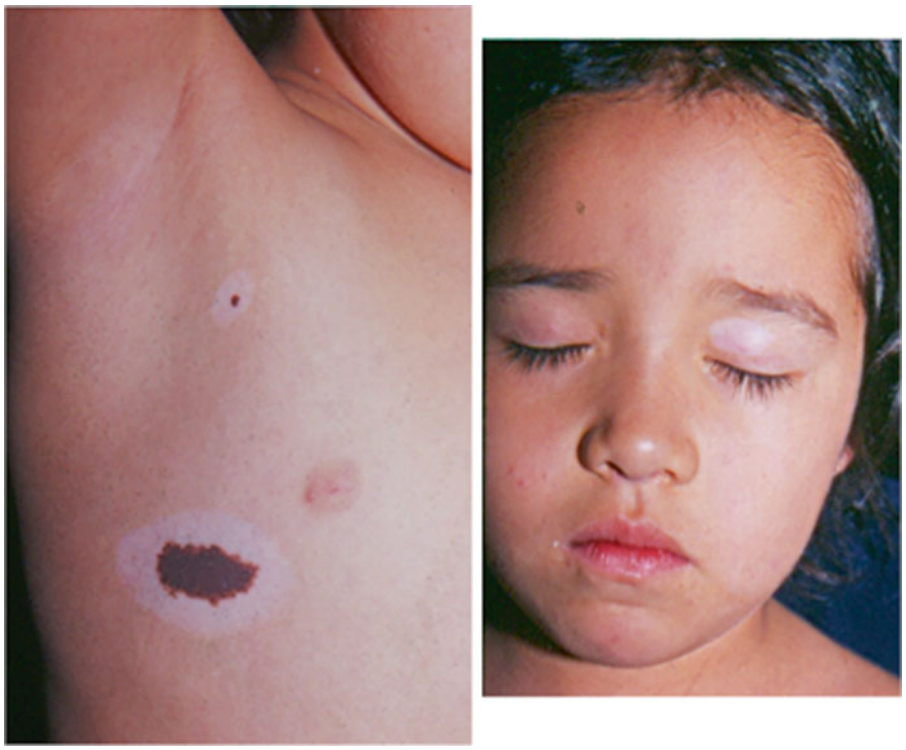

Fig. 27.7 "Halo nevus" phenomenon may be observed in congenital and acquired nevi. The patient has vitiligo as well

Small congenital melanocytic nevi (SCMN) may show junctional, compound, or dermal nevus patterns, and some can be histologically indistinguishable from common acquired melanocytic nevi [3, 48, 49].

Proliferative nodules occur in the reticular dermis as benign cellular melanocytic proliferations. Features that favor a benign course include blending of these cellular aggregates with the surrounding nevomelanocytes, low mitotic rate, absence of uniform high-grade cytological atypia, absence of inflammatory infiltrate, and absence of necrosis. Long-term follow-up of a large number of patients with a proliferative nodule has not been published. Thus, careful follow-up for any recurrence is recommended [5].

Dermatoscopy

Moscarella et al. [14] stressed that by dermatoscopy, the main pattern seen in CMN is the so-called "cobblestone pattern," consisting of large, angulated globules, resembling cobblestones.

Additional dermatoscopic criteria include perifollicular hypopigmentation, milia-like cysts, and the presence of coarse hairs (hypertrichosis). Dotted and comma vessels may also be apparent in some CMN [14, 50].

CMN on the head, neck, and trunk of children frequently exhibit a globular pattern, whereas those arising on the extremities (particularly the lower limb) often display a reticular pattern [50].

Treatment

- Excision of CMN is considered to reduce the chance of MM or for cosmetic reasons
- Benefits of early excision to prevent development of MM have not yet been proven
- Surveillance is a reasonable option
- Avoid extensive surgery that may result in deformity or compromised function
- Partial thickness removal strategies may result in better cosmetic outcomes but do not reduce the risk of MM when more aggressive surgical procedures are not practical

The treatment approach to CNM is the subject of continuing discussion, mainly because only the risk of tumor development on the cutaneous nevus can be reduced [9]. Excision of CMN before the development of malignant melanoma (MM) should be considered for two reasons: reduce the chances of MM development and cosmetic reasons [51].

If no neurocutaneous melanosis is present, most experts advise early and complete excision of large and giant CMN or at least to remove particularly striking or difficult to control areas at the end of the first year of life [9]. Hamm

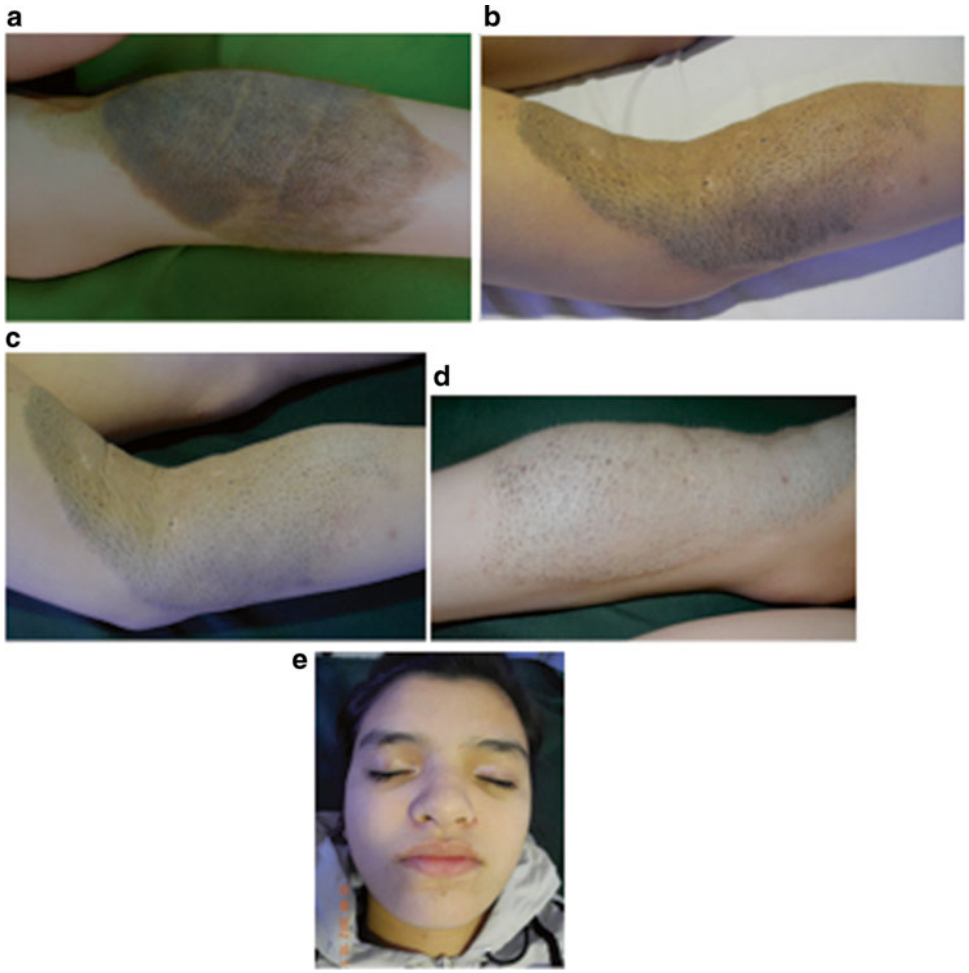

Fig. 27.8 (**a**–**d**) Note regression of a large congenital melanocytic nevus. Loss of color of the nevus and surface thickness. Note loss of hair color and hairiness within the nevus. Vitiligo like areas are noted within the nevus. (**e**) The patient developed vitiligo on distant sites. Note color loss on both superior eyelids

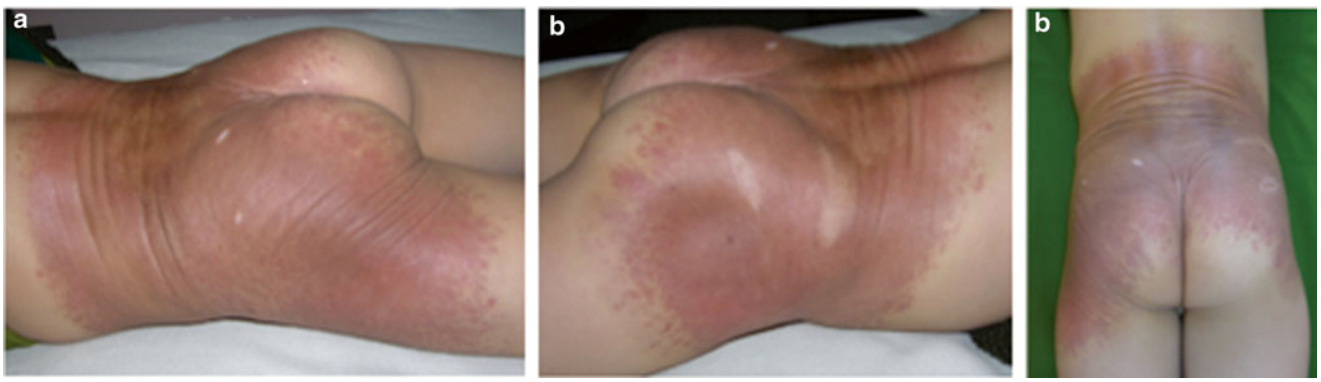

Fig. 27.9 (**a**–**c**) DHHN: Note hairless GCMN with peculiar ligneous appearance and regression signs

Removal of giant CMN is technically difficult, and complete removal is often impossible [9, 51].

Removal procedure can be classified into two main groups: full thickness and partial thickness. The first ones remove the epidermis, the entire dermis, and variable amounts of subcutaneous tissue. Whereas superficially ablative procedures, such as dermabrasion, serve primarily the purpose of cosmetic improvement and make sense only

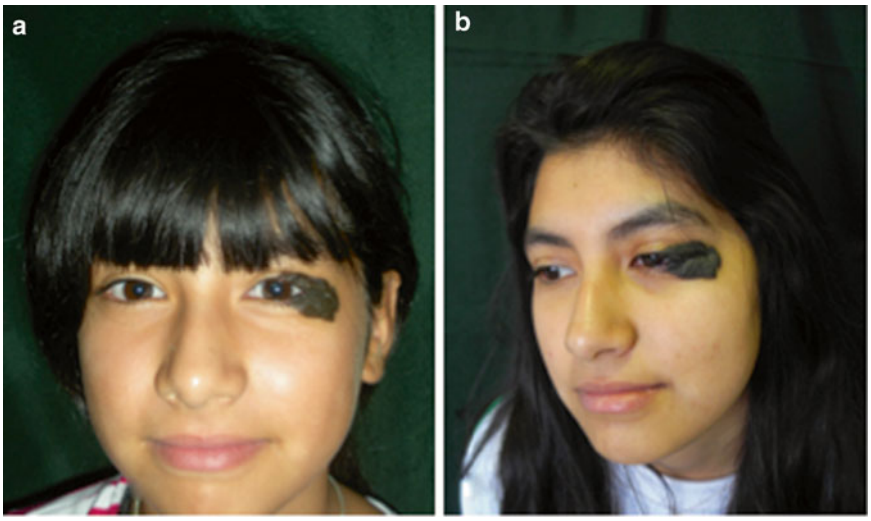

Fig. 27.10 (**a**, **b**) Divided nevus of the eyelid. Note increase of thickness and surface changes with age

in the first few months of life and in lesions that cannot be excised. Dermabrasion does not reach the deeper nevus cell layers; furthermore, it does not prevent hypertrichosis, which typically accompanies nevi. According to the current state of knowledge, laser treatment should be considered only in particular cases and special localizations (e.g., the face) (Table 27.5).

Independently of the surgical treatment, quarterly follow-up is recommended in cases of large or giant CMN [9, 51].

Given that the benefits of early excision over routine surveillance have not been proven up to date, surgery that is likely to result in significant deformity or compromised function should be avoided. Excision will do nothing to reduce the chances of extracutaneous MM or neuromelanosis. If the patient and or the doctor decided not to treat the CMN, clinical, dermatoscopic, and/or photographic follow-up is necessary [51].

Prognosis and Associations

- Malignant melanoma and other malignant tumors arising from CMN develop in the first decade of life in most cases
- Large and giant CMN may be associated with neurocutaneous melanosis (NCM)
- The symptoms of CMN are hydrocephalus, seizures, cranial nerve palsy, sensorimotor deficits, bowel and bladder dysfunction, and/or developmental delay and prognosis is poor
- Malformations of the central nervous system (CNS) are more frequent in GCMN (5–15 %)

Two main areas of concern associated with CMN are, first, the risk of melanoma development and, second, cosmetic and psychological issues [9, 14].

The malignant potential of CMN has been known for more than a century. However, it is becoming increasingly clear that the dimension of the risk of malignant degeneration differs widely on a case-by-case basis and depends on the size of the nevus, among other factors. The risk of malignant degeneration of small- and medium-sized CMN is low [9].

Cutaneous melanomas and other malignant tumors arising from CMN develop in the first decade of life in most of the cases. Melanomas develop in the deeper strata of the nevus and consequently are noticed later. Melanomas can develop from the nevus but also on other locations, for example, the central nervous system.

Large and giant CMN may be associated with neurocutaneous melanosis (NCM), a term that describes melanocytic proliferation (benign or malignant, nodular, or diffuse) within the leptomeninges and brain parenchyma, associated. It can affect different locations in the central nervous system, causing variable clinical manifestations, including death [7, 9, 52]. An important risk factor for this association is a large number of the so-called satellite nevi. Symptomatic NCM frequently manifest in the first 2–3 years of life with signs of raised intracranial pressure or spinal compression. In these cases the prognosis is poor. The symptoms are hydrocephalus, seizures, cranial nerve palsy, sensorimotor deficits, bowel and bladder dysfunction, and/or developmental delay [4, 53–56].

Malformations of the central nervous system (CNS) may be present and are more frequent in GCMN that overlie the dorsal medial body axis and/or have multiple satellites. MRI is recommended in the first 4–6 months of life [7, 9].

The risk that one of these complications may develop is estimated at 5–15 % for GCMN and is highest in the first 5–10 years of life [9]. Other associations of CMN have been described (Table 27.6).

Table 27.5 Treatment options

NO-TREATMENT	Follow-up: Clinical, Photography, Dermatoscopy

TREATMENT			
FULL THICKNESS EXCISION Complete Excision Serial Excisions		PARTIAL EXCISION PROCEDURES Dermatome Shaving Curettage Dermabrasion Chemical Peelings Cryotherapy Lasers Ablative / Pigment specific	
Advantages Reduction of nevus cells may reduce MM risk May improve cosmetic appearance	Disvantages Possibility of repigmentation on surgical scars, may complicate follow up May worse cosmetic appearance	Advantages Removes some CMN cells; might reduce the risk of MM Lasers: Ablative: precise depth of removal Pigment specific: can remove target melanosomes or melanocytes Better cosmetic outcomes	Disvantages Do not remove all nevi cells as full thickness excisions Scars May difficult detection of MM

Table 27.6 Associations of CMN. Modified from Marhoob et al. [67]

Syndromes associated with CMN	Other key features
Carney syndrome	Cardiac and cutaneous myxomas, endocrine abnormalities
Epidermal/Schimmelpenning	Linear epidermal/sebaceous nevi, CNS and MSK defects
Neurocutaneous melanosis	Leptomeningeal melanocytosis and obstructive hydrocephalus
Neurofibromatosis type 1 (possible association)	Cutaneous and plexiform neurofibromas, cafè-au-lait spots, Lisch nodules
Premature aging syndrome	Premature aging, short stature, birdlike facies, deafness
Occult spinal dysraphism/tethered cord	Spinal cord abnormalities, lipomas, vascular malformations

Ongoing Research

Pathogenesis

Mutations in NRAS, BRAF, and Tp53 have been described in CMN; however, its role in the pathogenesis is not clear. Kinsler et al. [7] proposed that a single postzygotic mutation in NRAS could be responsible for multiple CMN in a same individual, as well as, for melanocytic and nonmelanocytic CNS lesions. These mutations presumably lead to an excessive number of daughter cells bearing the mutation that migrates to subcutaneous, dermal and epidermal, as well as CNS locations. They suggest that mutations probably occur

in the developing neural crest or neuroectoderm. Their findings of NRAS mutations in neurological as well as skin lesions support a unifying causal mutation in these patients.

NRAS is an extensively characterized oncogene involved in the control of key signaling pathways [57–59]. Germline mutations in the RAS/RAF/MEK/ERK pathways give rise to a group of conditions now termed RASopathies, including Neurofibromatosis type 1, Costello syndrome, Cardiofaciocutaneous syndrome, Noonan syndrome, and Leopard, most of them harboring pigmentary abnormalities [7, 59, 60]. Mosaic RASopathies could also be recognized as part of the spectrum, as has been suggested for Schimmelpenning syndrome by Groesser et al. [61]. Children with CMN have characteristic facial features [62]. This finding has relevance as the neuroectoderm also contributes to the development of cartilage and facial bones. The germline RASopathies all have characteristic facial features, demonstrating the effect of RAS/RAF/MEK/ERK pathway imbalance on facial development [63]. Although speculative, it is feasible that the current finding of NRAS mutation mosaicism in individuals with multiple CMN could explain the facial similarities in this patient population as a result of a mutation in neuroectoderm cells affecting precursors involved in facial development. If these findings prove to be true we can include CMN within the mosaic RASopathies.

On Follow-up

Dermatoscopy

The target network, small globules, vessels, and follicles help to distinguish between small- and medium-sized CMN and acquired nevi with a sensitivity of 82.5 % and a specificity of 64 %. Other highlighted features included focal thickening of network lines, globules, skin furrow and/or perifollicular hypopigmentation, and satellite areas [4]. A limitation by this method is in distinguishing between early melanoma and proliferative nodules within CMN. Future research that enables this differential diagnosis will add a new field for dermatoscopy in the follow-up of these lesions.

Confocal scanning laser microscopy like dermatoscopy, the inability of confocal microscopy to reach the deep dermis, excludes important information for the follow-up of CMN [64, 65].

Illig et al. [66] reported a series of CMN measuring less than 10 cm in diameter that developed melanoma within the nevus. The histologic assessment revealed that melanoma in those nevi originates from the dermoepidermal junction, and none had an intradermal origin. Hence, confocal microscopy could have a roll in the follow-up of small- and medium-sized CMN. The depth of cell infiltration of CMN correlates with the size of the nevus. Technical improvement will probably result in better histological detail as well as in optical penetration depth to allow an increased visualization within the dermis. Also clinical-dermatoscopic-confocal microcopy studies will add clues for the better follow-up of CMN [63].

Summary

Genetic advance allow us to include CMN within the mosaic RASopathies. This will allow us to better understand the etiopathogenesis of these lesions, its associations, and complications.

Although a consensus has not been met, guidelines for the diagnosis and follow-up of CMNs have been published. Although the incidence of CMN seems to de higher in some races with pigmented skin, awareness of the need for sun protection and follow-up of these lesions are not widely known.

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Becker's Nevus

28

María del Carmen Boente

Abstract

Becker's nevus is characterized by the presence of a light or dark brown patch or plaque with a sharply outlined but irregular border that resolves into smaller pigmented spots, arranged in a checkerboard pattern. In male patients, the lesion may show increased hairiness after puberty. Becker's nevus is a fairly common condition, but often overlooked or misdiagnosed.

"Becker's nevus syndrome" represents one of the epidermal nevus syndromes and denotes the simultaneous occurrence of Becker's nevus and unilateral breast hypoplasia or other cutaneous, muscular, or skeletal defects. All of these anomalies tend to show a regional correspondence to the nevus and are mostly ipsilateral.

Keywords

Becker's nevus • Becker's nevus syndrome • Becker's pigmented hamartoma • Mosaicism

Introduction

- Becker's nevus is an organoid nevus reflecting mosaicism
- It is characterized by a hyperpigmented, often hairy macule with a sharp outline but irregular borders
- Becker's nevus is arranged in a checkerboard pattern, more often located in the upper half of the thorax

S.W. Becker first described Becker's nevus (BN) in 1949 as "concurrent melanosis and hypertrichosis in the distribution of nevus unius lateris"; it was subsequently named after him [1].

Other names given to this nevus are Becker's melanosis, pigmented hairy epidermal nevus, and Becker's pigmented hamartoma. Because melanocyte counts are not increased in this lesion, these names should be discouraged in order to avoid further confusion with a melanocytic lesion.

BN is an organoid nevus, reflecting mosaicism, that manifests as one or more lightly to deeply hyperpigmented, usually hairy patches or plaques, with a sharp demarcation from normal skin, but irregular borders. Lesions are arranged in a checkerboard pattern, more often located on the upper half of the thorax, shoulder, or arms. It can be seen in any part of the body. The association of this nevus with unilateral breast hypoplasia, muscle, skeletal, and/or skin anomalies has been named Becker's nevus syndrome. All of these anomalies tend to show a regional correspondence to the nevus and are mostly ipsilateral [2–4].

Epidemiology/Demographics

The prevalence of BN is not known, but a study involving 19,302 men (17–26 years old) showed that it is close to 0.52 % [5]. Hair density may be variable and may even be absent. In 5 % of the cases, BN is itchy, and in 25 % there is a history of severe sunburn prior to the lesion. There is a strong association with smooth muscle hamartoma [3–5].

A retrospective study was performed by Patrizi et al. in Italy, covering a 10-year period, to better define the clinical characteristics of the BN in childhood; they analyzed 118 cases and found that the BN was more frequent than other

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studies suggested and had similar predilection sites to those of adults but that hypertrichosis was rarely seen in the condition [1]. Contrary to expectations, the peak incidence of BN was observed not at puberty but at birth. No sex predilection was found in their study, in agreement with data reported by Happle and Koopman [6].

Most authors believe that isolated BN occurs more frequently in men than in women, with a 2:1 ratio. Happle and Koopman [6], however, stated that the true sex ratio may in fact be 1:1, because BN tends to be less conspicuous in women [4–7].

This nevus can occur in all races. It usually appears around puberty and in 75 % of instances it has appeared before the age of 15 years. Although in its classic form it is considered to be an acquired disorder, the occurrence of congenital Becker's nevus has been reported [7–10]. Familial cases can also occur [7, 9–13].

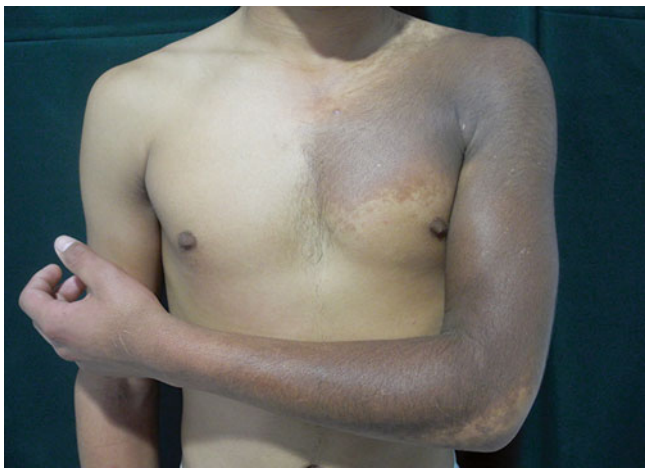

Fig. 28.1 Dark pigmented, hairy patch in a checkerboard distribution. Note thoracic asymmetry

Clinical Presentation

- BN is a congenital lesion noticed in childhood
- Is an organoid epidermal nevus characterized by light to brown patches in a checkerboard distribution
- Is an androgen dependent lesion, showing increase in hairness and color at puberty
- Histologically there are no nevus cells so there is no increased risk of malignant transformation

BN is usually first noticed in childhood, after sun exposure, as a grayish, light, or dark brown pigmentation on the chest, back, or upper arm, although it can be seen in any body site. It spreads in an irregular fashion until it reaches an area of 10–15 cm in diameter. The outline is sharply demarcated, irregular, and often surrounded by islands of blotchy pigmentation [3, 14] (Figs. 28.1, 28.2, and 28.3).

Within the group of epidermal nevi, it can be classified as an organoid epidermal nevus, arranged in a checkerboard pattern. It can be present as a single or as multiple lesions. The lesion represents a form of mosaicism; therefore, it is a congenital lesion with growth of the lesions near puberty because it is an androgen dependent nevus [3]. Near puberty the lesion becomes thicker and darker and in most of them dark, coarse hairs appear in the region of, but not necessarily coinciding with, the pigmented area [14] (Fig. 28.1).

Histopathologic features reveal epidermal thickening, elongation of the rete ridges, and increased pigmentation in the basal layer. There is no increase in number of melanocytes, and since there are no nevus cells, malignant transformation does not generally occur. Hair structures and smooth muscle fibers are usually increased in number [7, 14, 15].

The entity known as smooth muscle hamartoma could be into the clinicial as well as histopathological spectrum of BN.

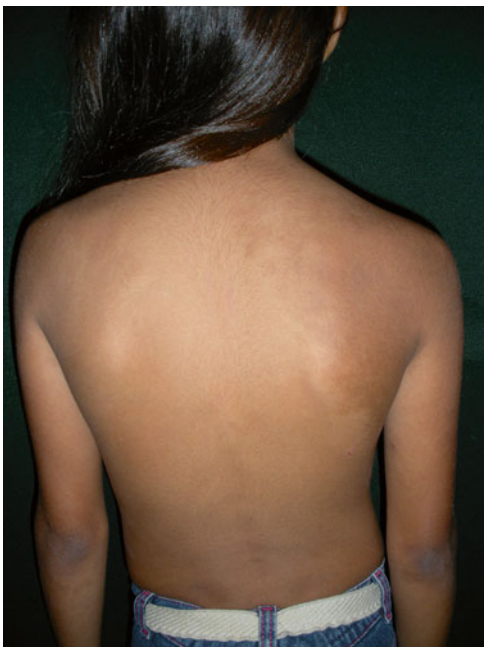

Fig. 28.2 Female patient. Note light hyperpigmented macule over the right shoulder and scapula. Note scoliosis

Treatment

BN is a benign condition; therefore, treatment is merely for cosmetic reasons. The most effective treatment is not been well defined. Traditional surgical excision usually is unsuccessful and may result in unacceptable scars. Lasers have been used for improving the pigmentary component as well as for reducing the associated hypertrichosis, with variable results 4, 7.

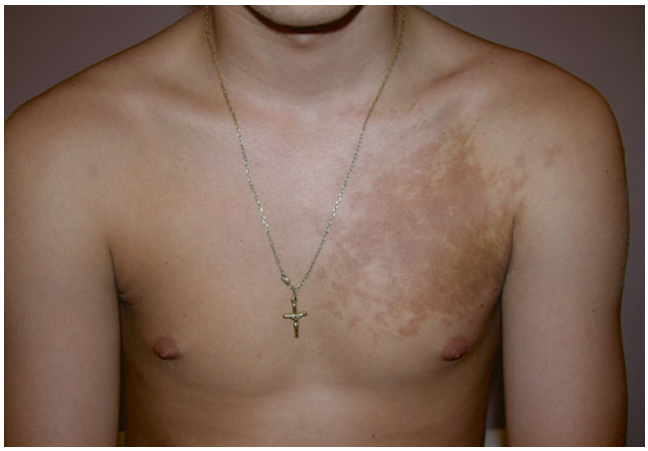

Fig. 28.3 Sharply demarcated, irregular brown macule surrounded by islands of blotchy pigmentation

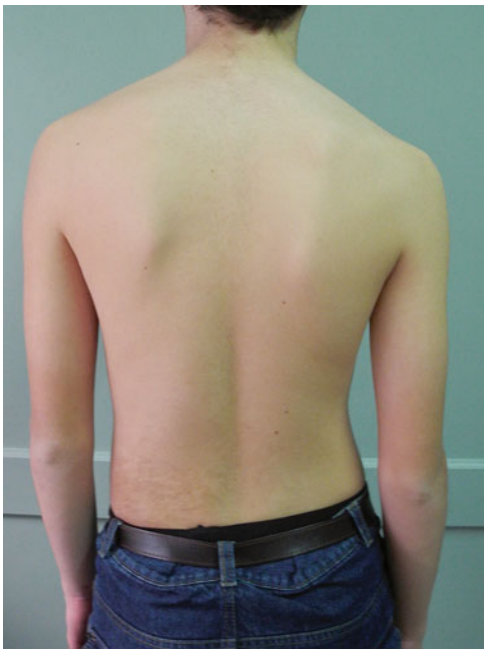

Fig. 28.4 Light brown patch on the left girdle (lumbar area). Note scoliosis

Trelles et al. [16] demonstrate the superiority of Erbium: YAG laser when compared to Q-switched Neodymium:YAG laser, showing complete clearance in 54 % of the patients. Moreno-Arias et al using intense pulsated light showed not very satisfactory results, with clearance of less than 25 % of the lesions [17]. Choi et al. showed a fair to excellent clinical response in 11 patients treated with long-pulsed alexandrite laser with mild to moderate side effects in some patients, consisting of hypopigmentation, skin texture change, and scar [18].

Lapidoth et al. reported the use of low fluence with high-repetition-rate diode laser hair removal as a safe and effective method for the management of hypertrichosis in Becker's nevus. No adverse events were reported [19].

Glaich et al. used a fractionated laser showing good response, without side effects [20]. In a study by Meester et al., an ablative 10,600-nm fractional laser therapy was moderately effective in patients with BN [21]; postinflammatory hyperpigmentation and relatively negative patient-reported outcomes still preclude ablative fractional laser therapy from being the standard therapy [22].

Prognosis and Associations

BN is an androgen dependent lesion; therefore, women and prepuberal boys merely show a hyperpigmented patch with bizarre outlines and mild or absent hairiness. In adult men the pigmented patch is darker and is covered by pronounced hypertrichosis [1, 4, 23].

The intralesional presence of acne and the occurrence of BN in a patient with accessory scrotum further reflect the pathogenetic role of androgens in the disorder. The increase in prevalence of pityriasis versicolor within the nevus may be explained by an increased sebum production. Increased number of androgen receptors, and androgen receptor messenger RNA, in the nevus compared with unaffected skin, has been reported [4, 24–26].

Moore et al. first reported the association of BN with hypoplasia of breast and pectoralis major muscle, characterizing one important aspect of this organoid epidermal nevus syndrome [27]. Although BN is more frequently reported in men, Becker nevus syndrome is reported more frequently in women because of the more noticeable feature of ipsilateral breast hypoplasia (Fig. 28.1). Other syndromic associations include asymmetric patchy hypoplasia of subcutaneous fatty tissue, supernumerary nipples, absence or hypoplasia of ipsilateral muscles, scoliosis, and skeletal anomalies of the thorax, as well as segmental odontomaxilary hypoplasia or dysplasia, depending of the localization of the nevus [15, 23] (Figs. 28.2, 28.3, and 28.4).

Although BN, and Becker nevus syndrome, usually occurs sporadically, as an autosomal dominant lethal mosaicism, some rare familial cases have been reported. This can be better explained by the genetic mechanism of paradominant inheritance [28]. Suppernumerary nipples occurring together with BN further support a paradominant trait [29]. Paradominance represents a mode of transmission that imitates dominant transmission for traits that are neither simply Mendelian nor entirely non-Mendelian [28]. Heterozygous gene carriers are usually phenotypically normal and therefore the gene can be transmitted without any clinical expression through many generations. The trait becomes evident only when a somatic

mutation occurs, resulting in a mosaic patch of cells showing loss of heterozygosity. These mosaic cells are either homozygous (resulting from mitotic recombination, gene conversion, or point mutation) or hemizygous (resulting from mitotic non-disjunction or a deletion) for the underlying mutation [30].

Summary

BN is an organoid epidermal nevus characterized by one or more hyperpigmented patches or plaques with well defined, but irregular outlines, arranged in a checkerboard pattern. Although predominates in the upper half of the thorax, all regions of the body may be affected. The sex ratio probably does not deviate from 1:1, and the preponderance of cases in males can be explained by the androgen dependence of this nevus producing a characteristic hypertrichosis, noted more in postpubertal men.

BN can be associated with breast hypoplasia. This syndrome has so far been reported more frequently in females because ipsilateral hypoplasia of breast is less conspicuous in male patients. Other cutaneous, skeletal, and muscular defects should also be investigated. Treatment of these nevi is only for cosmetic reasons. Laser for hair removal, pigmentation, and ablative lasers has been reported with variable success.

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Part VI

Inflammatory Skin Conditions and Dermatoses

Atopic Dermatitis in Pediatric Skin of Color

29

Aviva C. Berkowitz and Jonathan I. Silverberg

Abstract

Atopic dermatitis is one of the most common dermatologic diseases and affects a significant proportion of the pediatric population, both in the USA and worldwide. Children of many racial and ethnic groups are affected, but the specific role of this disease and how it affects these groups have been largely unexplored until recent years, and much still remains to be elucidated. This chapter will discuss the reported epidemiology of atopic dermatitis in pediatric skin of color. It will describe the diagnostic criteria and clinical manifestations of the disease in general, and will also explain the particularities that are present in different racial and ethnic groups, which are important for physicians to consider. The chapter will also focus on the available treatments and typical prognosis for atopic dermatitis, as well as the relevant special considerations that apply to patients with different ethnic backgrounds.

Keywords

Atopic dermatitis • Eczema • Pediatric • Race • Ethnicity • Epidemiology

Introduction

Atopic dermatitis (AD) is an inflammatory skin condition that is characterized by pruritus and chronic exacerbations. AD is one of the most common dermatologic disorders of childhood.

The clinical phenotype of AD results from a complex relationship between genetic and environmental factors. Many cases begin in infancy and can persist well into adulthood with significant morbidity. Recent efforts have been made to elucidate the impact of AD in various racial and ethnic groups. This chapter will review the current epidemiology, clinical presentation, prognosis, and treatment approaches for AD with special considerations for different ethnic and racial groups. Further, we will discuss relevant ongoing research and identify gaps in our understanding of AD in pediatric skin of color.

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Epidemiology

Racial and Ethnic Groups Reported to Be Affected
Caucasian, Black/African American, Asian/Pacific Islander, Hispanic/Latino, Native American, Middle Eastern

- AD affects a significant proportion of the pediatric population, both in the USA and worldwide, and the incidence is on the rise.
- Prevalence and severity may be increased in certain racial/ethnic populations, especially Blacks/African Americans, though more information on the subject is warranted.
- Certain factors have been found to be positively associated with AD, including socioeconomic status, urban area of living, and birthplace in the USA.

AD or eczema has been ranked by the World Health Organization's Global Burden of Disease study as the most disabling skin disorder worldwide [1]. The overall prevalence of

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childhood AD ranges from 0.3 to 20.5 %, with significant variation between countries and regions [2]. In general, AD is more common in industrialized countries and urban areas [3]. In the USA, the prevalence of AD is 10.7 %, also with significant statewide variation [3]. Of children in the USA with AD, approximately 26 % have moderate and 7 % severe disease [4].

Some controversy exists as to whether the prevalence of AD is truly increasing. Several studies have suggested as much, with similar trends found for asthma and hay fever. However, some argue that the definition and measurement of AD have been problematic in these studies, producing results that do not reliably distinguish between an actual difference in prevalence and differences in diagnostic procedures [5]. A recent study attempted to examine the trends in AD prevalence using subjects from the same study centers that participated in Phases One and Three of the International Study of Asthma and Allergies in Childhood (ISAAC I and III studies). The study determined that in children aged 13–14 years, prevalence seemed to plateau or decrease in some developed countries that previously reported high prevalence rates, such as the UK and New Zealand, while a number of developing countries, such as Mexico (except rural areas) and Kenya, demonstrated increased AD prevalence. In younger subjects, most participating countries showed a significant increase in AD symptoms [6]. Of note, a Mexican dermato-epidemiology study found dramatically higher rates of eczema in urban areas, but not rural areas [7].

Environmental factors play an important role in the prevalence of AD. In the USA, children born in other countries or regions were found to have dramatically lower risk of AD, though their risk increased after residing in the USA for 10 years [8]. This underscores the idea that environmental exposures may trigger disease even in late childhood or adolescence. A number of specific associations with AD prevalence point toward the role of environmental and behavioral factors, including living in a metropolitan area, socioeconomic status, level of parental education, and family structure [3]. Climate is an important driver of AD prevalence and regional variation thereof, such that a combination of higher temperatures and ultraviolet (UV) exposure and less indoor heating appear to have a protective effect [9]. Several mechanisms have been proposed to explain the effects of climate on AD, in which the structural protein, filaggrin, and UV exposure are prominently featured. Animal models have shown that low-humidity environments lead to reduced formation of water-binding free amino acids in the stratum corneum of the skin and reduced expression of filaggrin by an unknown pathway [10]. UV exposure may be protective against AD by inducing immunosuppression via leukocyte apoptosis and suppression of MHC Class II expression [11]. Furthermore, filaggrin and UV exposure may behave synergistically. UV radiation causes a metabolite of filaggrin, trans-urocanic acid, to be converted into the cis isomer which is immunosuppressive [12] and which may decrease the proliferation of *Staphylococcal* species [13].

There is also some evidence of an association between obesity, physical activity, and AD. While prior studies have established a connection between obesity and asthma, several recent studies have sought to determine whether a similar association exists for AD. Obesity was found to be positively associated with AD in both adults and children [14–16]. These findings illustrate the potential for weight loss as an adjunctive tool in AD prevention and management. Viewing television for 5 or more hours per day and vigorous exercise were both found to be positively associated with AD in adolescents [16]. One possible explanation for the latter is that vigorous physical exercise results in increased perspiration, which in turn, exacerbates pruritus and symptoms of AD. The consumption of fast food, at least three times per week, was recently found to be associated with an increased risk of severe AD in children and adolescents [17]. This observation raises significant public health concerns as it highlights yet another harmful consequence of the increasing global trend toward fast food consumption.

Several studies demonstrated that AD is more prevalent in Blacks and other racial/ethnic minorities. In London, children of Caribbean descent were twice as likely to have AD as White children [18]. In the USA, multiple studies found that children and adolescents of African-American/Black race had significantly higher odds of AD compared to Caucasians/Whites [3, 9]. Studies have also suggested that AD may present with greater severity in certain groups, especially Black children [19]. The increased prevalence and severity of AD in Black children is likely multifactorial in nature, including intrinsic, behavioral, and environmental factors. Black subjects were found to have lower levels of skin ceramides than Asians and Caucasians [20] and higher levels of transepidermal water loss than Caucasians [21], both of which may contribute toward AD [22, 23]. African Americans were also observed to have larger mast cell granules [24], which may have an impact on the perception of pruritus. Several of the abovementioned factors associated with AD, including fast food diet, decreased physical activity, and obesity, are more prevalent in the African-American population [25–27].

While it is clear that AD has a significant effect on the lives of various minorities, these groups were noted to be considerably underrepresented, comprising only a small percentage of participants in clinical trials for AD over the last decade [28]. Further research is much needed on the epidemiology, pathomechanism, clinical course, and treatment response of AD in skin of color.

Clinical Presentation

- The three stages of AD, divided according to time of onset, are infantile, childhood/adolescent, and adult. They are generally characterized by acute, subacute, and chronic lesions, respectively.

- AD is characterized by pruritus and xerosis, serosanguinous discharge, erythematous plaques, with lichenification following chronic rubbing and scratching.
- People of different racial and ethnic groups may have a somewhat unique pattern of presentation, which may pose a challenge to physicians.

AD can be divided into three subsets, based on age of onset: infantile, occurring from infancy to age two; childhood/adolescent, from 2 years old to 12 years old; and adult, occurring after 12 years. Approximately 60 % of cases appear during the 1st year of life and about 85 % begin in the first 5 years of life. Many cases improve, with 40 % of children achieving remission before reaching adulthood [29]. AD has been demonstrated to be slightly more common in females in some studies [30].

Diagnostic Criteria

AD has a rather broad differential diagnosis as it can appear similar to a number of other skin conditions. It is important that these are excluded when making the diagnosis. Hanifin and Rajka formulated a list of diagnostic criteria in 1980 [31]. They proposed that one must have three or more major criteria and three or more minor criteria in order for a diagnosis of AD to be made. The criteria are listed in Table 29.1.

Table 29.1 Hanifin and Rajka criteria for AD

Major Criteria
- Pruritus
- Typical Morphology and Distribution
  - Flexural lichenification in adults
  - Facial and extensor involvement in infancy
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria
- Xerosis
- Ichthyosis/hyperlinear palms/keratosis pilaris
- Immediate skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency for cutaneous infections
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital folds
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pytiriasis alba
- Anterior neck folds
- Pruritus when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food hypersensitivity
- Course influenced by environmental and/or emotional factors
- White dermatographism or delayed blanch to cholinergic agents

Williams et al. abridged these criteria and proposed the UK Working Party's Diagnostic Criteria for AD [32]. The criteria are listed in Table 29.2.

Table 29.2 UK working party's diagnostic criteria for AD

Must have:
Evidence of pruritic skin, including parental report of a child rubbing or scratching

Plus 3 or more of the following:
- History of involvement of skin creases, including antecubital fossae, popliteal fossae, neck, areas around eyes, fronts of ankles
- History of generally dry skin within the past year
- Symptom onset under age 2 (not used if child is under 4 years)
- Visible evidence of dermatitis involving flexural surfaces (or dermatitis affecting the cheeks, forehead, and extensor surfaces in children under 4) (modified from Williams [32])

Clinical Features

Infantile AD is generally characterized by acute skin lesions with erythematous and edematous papules and plaques, accompanied by oozing, vesicles, and crusts. There may also be subacute lesions, which are erythematous with fine scaling and less oozing and crusting. The lesions typically appear on the cheeks, neck, scalp, trunk, and extensor surfaces of the infant, usually sparing the diaper area (Fig. 29.1).

Childhood AD is usually characterized by subacute to chronic lesions. Chronic rubbing and scratching leads to skin thickening and accentuation of skin lines, known as lichenification. Affected areas classically include flexural areas of the body, such as the antecubital and popliteal fossae, neck, posterior auricular area, wrists and ankles, as well as the face, hands, and feet. Nodular, prurigo-like lesions can also develop in some cases (Fig. 29.2).

Intense pruritus is the most prominent feature of the disorder and can be severe, causing flares, exacerbations, and chronic excoriations of the skin. For this reason, AD is referred to as the "itch that rashes". Itching and scratching leads to secondary skin changes, which contribute to disruption of the epidermal barrier, perpetuating the disease and ultimately worsening the "itch-scratch cycle" [30]. In severe cases of the disorder, especially those whose disease persists into adulthood, disease may even progress to generalized erythroderma [29].

Many children have improvement of their AD in the summer and flare during the autumn and winter, possibly due to a combination of the therapeutic effect of UV rays and greater humidity in the former and low humidity and exposure to indoor heating in the latter [30]. On the other hand, many children report itch with sweating [33], which is often problematic in the summer months.

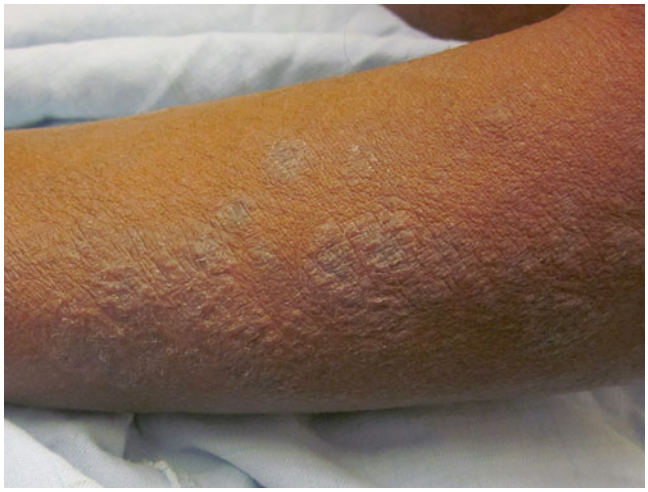

Fig. 29.1 Lichenoid atopic dermatitis on the forearm of a Hispanic male

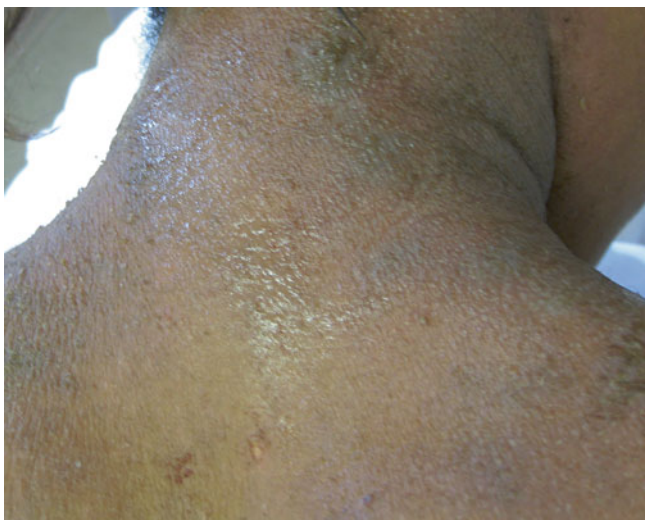

Fig. 29.2 Chronic lichenification on the neck of a teenage African American female with atopic dermatitis

Associated Features

Filaggrin is a structural protein which plays an important role in maintaining the integrity of the epidermal barrier. An intact epidermal barrier limits transepidermal water loss as well as the inflow of irritants and pathogens. Filaggrin is one of the last components to be incorporated into the formation of the cornified envelope of the epidermis, which is chiefly made up of the outer membranes of terminally differentiated keratinocytes [34]. Subsequent to its integration into the stratum corneum, filaggrin is also broken down into a number of hydrophilic amino acids and other components which together make up natural moisturizing factor (NMF) [35], an important substance in preserving skin hydration. As such, filaggrin (FLG) loss-of-function gene mutations lead to a deficiency of NMF [36], which likely contributes to xerosis in AD [37]. A number of FLG mutations have now been identified and have been shown to be a risk factor for AD [38, 39]. These mutations are rather common, detected in up to 10 % of western European and North American populations [40] and AD affects 42 % of mutation carriers [41]. A few studies have attempted to determine the prevalence of mutation in different racial and ethnic groups [42–44]. One pediatric cohort study found that among all patients with at least one variant of FLG mutation, 27.5 % were white and only 5.8 % were African-Americans [45].

Xerosis, or dry skin, is present in most cases of AD and is often accompanied by fine "dry" scale. One case series found that xerosis was present in 100 % of children with AD at 2 years of age [33]. Xerosis is usually worse in the winter, likely secondary to low indoor humidity. The etiology of xerosis in AD is multifactorial, including decreased epidermal hydration in conjunction with increased transepidermal water loss through a defective epidermal barrier [46] and lower levels of natural moisturizing factor secondary to filaggrin mutations [37].

Ichthyosis vulgaris is a condition characterized by extreme white-brown scale of the skin, especially on the lower extremities. Ichthyosis vulgaris is also caused by similar mutations of the filaggrin gene as those which cause AD [37].

AD is often accompanied by one or more atopic disease. In the USA, 25.1 % of children with AD reportedly had a history of asthma, 34.4 % had hay fever, and 15.1 % had food allergy [4]. Children with severe AD are more likely to have atopic disease than those with mild AD [4]. There are several physical signs that may serve as clinical clues of atopic disease, such as Dennie-Morgan lines that are horizontal skin folds under the lower eyelids; transverse nasal crease or "allergic salute" from rubbing of an itchy nose in hay fever, and "allergic shiners" that result from darkening of the periorbital areas secondary to edema in hay fever are common [47].

Several other dermatologic findings are associated with AD. In order of frequency, from highest to lowest, hyperlinear palms, keratosis pilaris, pytiriasis alba (hypopigmented, scaly patches, commonly occurring on the cheeks but can occur at virtually any body site), and white dermatographism also frequently affect patients with AD [33] (Fig. 29.3).

A lower irritant threshold is also associated with AD and it is hypothesized that this is due to intrinsically hyperreactive inflammatory cells [48]. A filaggrin deficient animal model provides further support for the notion that a defective epidermal barrier reduces the inflammatory threshold to common topical irritants [49]. Irritant reaction to various consumer items is also common in AD; many patients, especially women, have reported adverse skin reactions to scented products in several studies [50, 51].

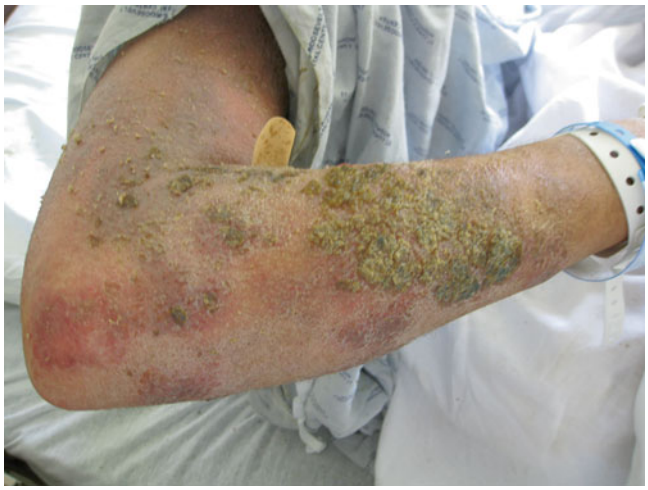

Fig. 29.3 Superinfected atopic dermatitis with oozing and crusting

Complications

According to Hanifin and Rajka's list of minor diagnostic criteria, AD patients have increased risk of skin infections in general. *Staphylococcal (S.) aureus* has been shown to colonize the skin of most patients with AD [52]. It is thought that super-antigens released by *S. aureus* contribute to AD flares and perpetuate active lesions [53]. Alternatively, inflammation in AD may predispose toward greater colonization by *S. aureus*. Impaired epidermal barrier and decreased naturally occurring antimicrobial peptides may predispose AD patients to more infections [54]. The rate of bacterial or viral infections found in an inpatient study was approximately 30 % for AD patients, in contrast to 6.7 % of those with psoriasis [55]. Interestingly, children with AD were also found to have increased rates of extra-cutaneous infections, including *Streptococcal* pharyngitis, colds and sinus infections, urinary tract infections, and recurrent otitis media, among others. These findings suggest that an element of immune dysfunction may contribute to the pathogenesis of AD and an overall increased susceptibility to infection [56]. There is some controversy as to whether AD patients have an increased risk of infection with methicillin-resistant *S. aureus* (MRSA) versus methicillin-sensitive *S. aureus* (MSSA) strains. It has been suggested that AD patients may be more susceptible to MRSA infection since anti-*Staphylococcal* antibiotics are often a part of their long-term treatment regimen [57]. Several recent studies found a low rate of MRSA in AD patients [58] and determined that children with AD were actually less likely to be infected with community acquired MRSA than the general outpatient pediatric population [59]. On the other hand, the prevalence of MRSA in AD children colonized with *Staphylococcal* species was determined to be between 18.3 and 30.8 % in other studies [60, 61] and it was concluded that this could present a significant reservoir of MRSA in the population [60].

Herpes simplex virus may trigger eczema herpeticum, widely disseminated viral super-infection of eczematous skin. Classically, monomorphic, umbilicated vesicles form especially on the head, neck, and trunk. These vesicles later evolve into "punched out" crusted erosions. It is usually accompanied by fever and lymphadenopathy and may spread to various organs including the eyes and brain if not treated appropriately with systemic antiviral therapy such as acyclovir [62]. Clinicians from one German hospital found a dramatic increase in incidence of this complication between 1969 and 1981 [63]. Infection with molluscum contagiosum can also be widespread with numerous umbilicated papules, though without systemic manifestations [62].

AD has a major impact on patient quality of life. Patients with AD were found to have significantly lower scores measuring quality of life compared to healthy control subjects and the general population [64]. A significantly smaller percentage of pediatric patients with AD in the USA identify as being in overall excellent health compared to those not affected with AD (55.2 % versus 63.4 %) [4]. Pruritus often poses a significant challenge and may be so severe as to cause sleep disturbances, with 10.8 % of US pediatric AD patients reporting at least 4 nights per week of impaired sleep [4]. Repeated sleep deprivation results in daytime fatigue, decreased capacity to complete daily tasks, reduced ability to function at school or work and may impair overall behavioral and psychological development in children. Patients may also suffer from psychological distress and a feeling of social stigma and may experience both functional and social limitations. In a community survey of teenagers and adults with AD, many patients reported limitations in activities of daily living, the most common of which was clothing choice, reported in 35 % of respondents. Limitations in social functioning and self-perception were also reported, with 20–25 % of participants declaring feeling embarrassed or angry about their appearance. In those with severe disease, 18 % often or always felt uncomfortable in group settings and 16 % were less satisfied with personal relationships [65].

Daily treatment regimens require a significant time commitment and may place a burden on home and family life, both financial and emotional. The financial implications of AD encompass direct costs such as out-of-pocket payment for various skin care products, medications, visit copays, and purchase of special clothing, as well as indirect costs, including absences from school or work [66]. A total of approximately $213 is spent per patient every year on emollients and over-the-counter medications [65].

There may also be an association between childhood AD and mental health disorders, including attention deficit (hyperactivity) disorder, depression, anxiety, conduct disorder, and autism [67–72]. Further, more severe AD appears to be associated with even higher prevalences of these disorders.

When the lesions of AD resolve, they can leave pigmentation alterations in their wake. Both hyper and hypopigmentation changes occur. This is especially true in the case of patients of different ethnic and racial groups with naturally darker skin and can be a source of much emotional distress [29]. Pityriasis alba is another pigmentation disorder that may be associated with AD. It is characterized by asymptomatic, hypopigmented, poorly demarcated, patches, usually on the face. Its etiology is somewhat controversial, though studies have linked atopy and xerosis with its pathogenesis [73]. In a clinical survey of 56 Korean patients with pityriasis alba, 18 % were found to have a history of AD [74]. In a histopathological analysis of samples from these patients, a reduced number of melanosomes within keratinocytes and reduced pigment in the epidermis were found. Daily frequency of bathing and water temperature were found to correlate positively with the presence of pityriais alba in a retrospective study, which provided support for the notion that xerosis, as in AD, may be an important aspect of its pathogenesis [75].

With longstanding disease, ocular complications can also arise, including keratoconus, keratoconjunctivitis, uveitis, and anterior and posterior subcapsular cataracts [29]. These complications have been well described in adults, with a frequency in AD between 25 and 50 % [76–78]. The severity of AD positively correlates with the development of ocular complications [79]. Posterior subcapsular cataracts are slightly more common; however, anterior subcapsular cataracts are more specific to AD [80]. Less is known about the prevalence of ocular complications in childhood AD. In a prospective study of 59 children with AD, 23 % of participants had a form of ocular disease associated with AD [81]. The majority of these cases were asymptomatic benign papillofollicular conjunctivitis, but findings also included one case each of bilateral nuclear cataract, purulent bacterial conjunctivitis, and chronic atopic blepharoconjunctivitis. These findings suggest that the occurrence of severe ocular complications of AD is rare in children with moderately severe disease.

Clinical Presentation and Special Considerations for Skin of Color

The classical presentations of AD are essentially the same across various racial and ethnic groups. However, there are a number of distinguishing features that are more characteristic of skin of color and must be considered. First, erythema is not as pronounced on more darkly pigmented skin. Erythema in skin of color often appears violaceous. Second, many patients of Black, African, and/ or Afro-Caribbean descent have papular/follicular eczema and/or lichenoid lesions. Indeed, 54.1 % of patients with AD in a region of southeastern Nigeria were found to have papular lichenoid lesions [82]. This can present an obstacle to a physician making the diagnosis and/ or attempting to assess the severity of AD, as erythema is a characteristic that is included in a number of the popular scoring tools, including SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index). This phenomenon could lead to a delay in diagnosis and treatment and, ultimately, more severe disease at presentation [19, 23]. When the lesions of AD resolve, they can cause persistent dyschromia or pigmentary alterations. These are almost always more pronounced in patients of racial and ethnic groups with darker skin [23].

Papular eczema presents with a pattern of small, distinct papules, especially on the trunk, as opposed to the more conventional patches and plaques and can present with severe pruritus. This particular morphology has been observed to be more common in skin of color [82, 83], as is a pattern of perifollicular accentuation [84]. In the Nigerian study, 70.3 % of patients had a scattered, often perifollicular, micropapular rash, on the extensor aspects of the joints. In a series of case reports, investigators identified three children with AD, two of which were African American, who developed prominent, pruritic, follicular papules in the periumbilical area as well as on the flexural areas of the arms and legs [85]. Such a pattern should alert the physician to the diagnosis even if other signs have not yet made their appearance.

Asian patients may present with "sandpaper-like lesions" on their extensor surfaces, wrist dermatitis, and hyperkeratotic papules as accompanying features [86]. African-American children and adolescents often present with lesions on the extensor surfaces of the body as opposed to the more traditional presentation of flexural involvement in this age group [18, 23]. Dennie Morgan lines are more commonly noted in patients of color, even in those without AD [87]. Ichthyosis vulgaris has also been reported to be more common in patients of color [82].

Treatment

- The cornerstones of AD therapy are protecting the integrity of the epidermal barrier by using emollients, avoiding triggering factors and implementing gentle skin care
- Topical anti-inflammatory agents, including corticosteroids and calcineurin inhibitors, are first-line therapy for AD.

- Many cases can be managed with emollients and topical therapy, but systemic anti-inflammatory therapy and other adjunctive treatments may be necessary.
- It is important not to undertreat and to initiate appropriately aggressive treatment plans to gain control and maintain remission of disease.

The management of AD requires a multi-tiered approach, which includes managing acute flares, as well as maintenance therapy to prevent the occurrence of future exacerbations. First and foremost, an extremely important aspect of therapy is education. Helping patients and families understand the nature of the disease, explaining the importance of good skin care, and avoidance of irritants and instruction on proper application of medications are all critical in creating a successful partnership, which optimizes the treatment and control of this disorder. Offering emotional support and directing families to helpful resources and support groups can help provide them with the tools they need to deal with the challenges of this condition.

Current treatment places an emphasis on avoiding potential trigger factors, skin hydration, and the repair and protection of the epidermal barrier, the disruption of which seems to play a large role in the pathogenesis of the disease. Mild cases can usually be treated with continuous application of emollients and low potency topical corticosteroids during flares. Moderate to severe cases require higher potency corticosteroids and other anti-inflammatory medications and, possibly, other adjunctive therapies. Usage of twice-weekly corticosteroids can be helpful in the maintenance of clear skin for children with frequent flares [88]. A summary of available treatments is outlined in Table 29.3.

Table 29.3 Treatments for atopic dermatitis

Lifestyle modification:
Limit bathing time to 15 min
Do not use very hot water for bathing
Use fragrance-free, gentle cleansers
Avoid known allergens
Avoid overheating
Use of humidifiers
Use mild clothes detergents
Wear soft, itch-free fabrics
Manage stress

Skin hydration and epidermal barrier repair:
Regular application of emollients, especially ointments or thick creams
Application immediately after bathing

Anti-inflammatory therapy:
- *Topical Anti-inflammatory Therapy*
  - Topical Corticosteroids
    Low potency for mild cases, face, and intertriginous areas
    Mid-high potency for moderate to severe/refractory cases
    Application immediately after bathing, before emollients
    Wet wrap technique for enhanced effect
  - Topical Calcineurin Inhibitors
    For topical corticosteroid failure and for face and intertriginous areas
    Pimecrolimus 1 % cream for mild-moderate disease, ages 2 and over
    Tacrolimus 0.03 % ointment for moderate-severe disease in children over 2
    Tacrolimus 0.1 % ointment for moderate-severe disease in adults
- *Systemic Anti-inflammatory Therapy*
  - Systemic Corticosteroids
    Short course for severe case refractory to topical therapy

Pruritis control:
Oral antihistamines at bedtime
Ice
Moisturizers with menthol, phenol, or topical anesthetic

Antimicrobial therapy:
- *Decolonization*
  - Bleach baths
  - Intranasal mupirocin
- *Treatment of Superinfection*
  - Topical/oral antibiotic treatment

Other therapies:
For severe, refractory cases
- *Phototherapy*
  - Narrowband-UVB for chronic, moderate disease
  - UVA1 for acute exacerbations and severe disease
- *Systemic Immunomodulatory Therapy*
  - Cyclosporine
  - Azathioprine
  - Mycophenolate Mofetil
  - Methotrexate
- *Targeted Molecular Therapy*
  - Omalizumab
  - Rituximab
  - Mepolizumab

Food allergy testing
Food allergy workup in a selective subset of patients
Food allergen avoidance if workup is positive

Alternative therapy:
Chinese herbal therapy
Dietary lipid supplements

Avoidance of Trigger Factors

There are numerous factors that can potentially exacerbate AD and these should be avoided in patients as much as possible. Excessive bathing with very hot water, low indoor humidity, and perspiration can all cause decreased skin hydration and contribute to disruption of the epidermal barrier [89]. Indoor humidity drops precipitously with prolonged use of indoor heating. Thus, patients can be counseled to lower the thermostat by a few degrees and open the window to allow naturally humid outdoor airflow. Some patients may benefit from using a cool-mist humidifier; however, evidence is lacking for their effectiveness [90]. Individuals with AD have a lower threshold for itch and may be sensitive to overheating, wool or other rough fabrics, and harsh soaps and detergents; other known allergens should be avoided as well [91]. The role of aeroallergens such as dust mites have not been clearly defined as yet [91]. Emotional distress has also been shown to play a role in disease exacerbation [89]. Racial and ethnic differences in relation to various trigger factors have not been described.

Maintaining Skin Hydration

Continuous skin hydration with emollients is a crucial component of therapy for AD as it helps restore essential lipids in the skin and contributes to the integrity of the epidermal barrier. Hydration is best accomplished via ointments, which have high lipid content, applied immediately after a lukewarm bath or shower to seal in moisture ("soak and seal" method). However, patient preference and compliance must be taken into account. Some patients may dislike the greasy feel of ointments and prefer thick creams with a low water content. This can be a viable option, especially in those with milder disease. Lotions have a high water content and can exacerbate xerosis by evaporation from the surface of the skin and are generally discouraged. Products with added ceramides or natural moisturizing factor ingredients may replete deficient barrier elements for some children of color. Emollients should be applied twice daily, covering the entire surface area of the body. Scented varieties or those containing potentially irritating ingredients should be avoided [91]. Topical medications should be applied before emollients.

Anti-inflammatory Therapy

Topical Anti-inflammatory Therapy

Topical corticosteroids are the mainstay of AD therapy, especially for acute flares. These agents reduce inflammation by suppressing the expression of certain transcription factors and pro-inflammatory cytokines and act on a number of immune cells [92]. The goal of therapy is daily use of an agent potent enough to bring about resolution of the flare and, possibly, subsequent tapering of the medication to every other day use until maintenance therapy with intermittent topical corticosteroids is initiated. Low potency corticosteroids such as hydrocortisone 1–2.5 % cream or ointment are appropriate for infants and children with mild disease. Medium potency ointments, such as fluocinolone 0.025 %, fluticasone proprionate 0.005 %, or triamcinolone 0.1 % are commonly used for more moderate to severe disease. For refractory cases, higher potency ointments may be used for a brief period of time with a transition to lower potency options when the worst of the flare has calmed. High potency ointments are particularly useful in areas with thick, lichenified plaques and for lesions on the palms and soles. Use of these agents, especially long-term use, is generally avoided in treating the face and skin folds, because of the potential side effects, which includes skin atrophy [91]. Maintenance therapy for up to approximately 16 weeks after a flare, with intermittent use of topical corticosteroids, may help to reduce relapses [93]. The ointment vehicle of these agents acts as its own emollient, and, like other emollients used for basic, daily skin care, should be applied immediately after bathing to enhance skin hydration.

Wet wrap therapy may be a useful technique to incorporate for acute flares, especially in cases of severe or refractory AD [91]. With this approach, topical medication and emollients are applied to the patient's skin. A layer of damp material (gauze, cotton pajamas, etc. soaked in warm water) is then wrapped around the affected area, immediately followed by another layer of dry material. The wraps are left on overnight and may be used with once-daily topical treatment for several days. This form of treatment is beneficial in that it enhances skin hydration and acts as a physical barrier to scratching. It also serves as an occlusive dressing which allows more effective penetration of topical medications into affected skin [91].

Two topical calcineurin inhibitors are currently available as effective second-line treatment options for AD in patients over age 2 [94]. Tacrolimus 0.03 % and 0.1 % ointment are FDA approved for moderate to severe disease. Pimecrolimus 1 % cream is often used for mild to moderate disease. These agents block the pro-inflammatory downstream effects of calcineurin, which activates T-cells by upregulating expression of interleukin-2. Calcineurin inhibitors do not result in cutaneous atrophy as may occur with topical corticosteroids, and thus, are ideal for use on the face and intertriginous areas. They may also be used in individuals with frequent exacerbations who would otherwise need constant steroid treatment [91]. There is data in the literature to indicate that pimecrolimus is equally efficacious in all races and ethnicities for mild to moderate disease [95]; however, tacrolimus may be more effective at the 0.1 % concentration for children of color [96]. Their major side effect is a burning sensation at the application site, which is more pronounced with tacrolimus and may subside with ongoing use. The burning sensation is often worse when tacrolimus is applied on wet skin, which precludes it being used in a "soak and smear" approach. Another, theoretical side effect is increased risk of malignancy for which the FDA has placed a black-box warning, although this matter is highly controversial and has not been well elucidated.

Systemic Anti-inflammatory Therapy

Occasionally, systemic corticosteroids may be used in a case of severe disease which is unresponsive to appropriate treatment with topical therapy. A short course may be implemented with careful monitoring for potential side effects. The patient should be switched to topical therapy or other systemic therapies that are more suitable for long-term use as soon as possible to avoid these side effects as well as rebound flares [97]. In our experience, it is common for patients with chronic moderate to severe AD to rapidly flare upon tapering and discontinuation of prednisone and other oral corticosteroids. Oral corticosteroid therapy,

therefore, may become addictive and should be used with caution.

Pruritus Control

Adjunctive pharmacotherapy to treat pruritus may be important in controlling the itch-scratch cycle of AD. This is usually accomplished with sedating antihistamines, given at bedtime, which are particularly useful in patients who suffer from difficulty falling asleep or have poor sleep efficiency due to itchiness [98]. Applying ice or topical agents that contain menthol, phenol, antihistamines, pramoxine, or topical anesthetics may provide some relief. However, some of these topical agents work via the creation of distracting sensations, which ultimately may enhance irritation [30]. There is currently only modest objective evidence demonstrating efficacy of these agents [99]. Currently, the most effective treatments for itch in AD are topical or systemic anti-inflammatory agents [100].

Antimicrobial Therapy

The preponderance of individuals with AD are colonized with *Staphylococcus aureus* and bacterial counts increase with disease flares [101–103]. Bleach baths have been developed to treat prophylactically with the goal of eliminating *Staph* colonization. One cup of standard household bleach is diluted in a lukewarm bath with 40 gallons of water twice weekly. This adjunctive therapy resulted in improved symptoms on the trunk and extremities [104, 105]. However, the bleach may provoke itching or burning of the skin, especially in those with open cuts, excoriations, or fissures. Thus, bleach baths may be better suited for maintenance therapy rather than for acute AD flares. Topical mupirocin, applied intranasally, is widely used to decolonize the nose, particularly in those with a propensity for impetigenization. However, combination topical mupirocin and corticosteroids offered no advantage over topical corticosteroid monotherapy [106]. Therefore, use of mupirocin for the treatment of AD per se is not recommended. In cases of bacterial superinfection, appropriate topical or oral antibiotics are warranted.

Phototherapy

When topical therapies are insufficient for adequate control of disease, ultraviolet light therapy can be added to the treatment regimen, though multiple sessions are usually required for effect [91]. UV therapy acts to suppress DNA synthesis and leads to decreased numbers of dermal T-cells and Langerhans cells. It also stimulates the expression of cytokines that play a role in immune suppression [107]. Potential side effects include erythema, skin irritation and paradoxical exacerbation of AD, skin aging, and carcinogenesis with prolonged exposure. Narrowband UVB has become the preferred modality for chronic, moderate AD, and may have a more favorable side effect profile, and high dose UVA1 is recommended for more severe cases as well as acute flares [108, 109].

Immunomodulatory Therapy

Several immunomodulatory agents are used off-label for moderate to severe refractory cases of AD. Oral cyclosporine has been shown to be the most consistently, reproducibly, and rapidly effective mode of treatment for severe AD with significant improvement of lesions and pruritus in both adults and children [110–112]. The dose given should be the minimum that is required to produce an effect. Patients receiving cyclosporine must be closely monitored for dangerous side effects, such as impaired renal function and increased blood pressure. Other side effects include dizziness, gingival hyperplasia, hypertrichosis, hyperkalemia, hypomagnesemia and interactions with numerous other medications. The presence of these side effects is an indication to discontinue the medication.

Methotrexate, azathioprine, mycophenolate mofetil, and tacrolimus are also potential treatment options for moderate to severe disease. While they do not seem to be quite as effective as cyclosporine, they may boast a better safety profile [112]. Something to consider with regard to azathioprine, however, is that some individuals are more susceptible to its major side effect of bone marrow toxicity because of a naturally decreased level of the enzyme thiopurine methyltransferase (TPMT). Before initiating therapy, an effort should be made to determine the enzyme activity in the patient and to modify the dose accordingly [113]. Therapeutic effect with azathioprine or mycophenolate often does not begin until approximately 4–6 weeks of treatment and does not reach its peak until 2–3 months of treatment [111].

Targeted Molecular Therapy

A handful of "biologics" have been studied as potential treatment options, some with controversial findings. Omalizumab is an anti-IgE monoclonal antibody, which is FDA approved for asthma. Rituximab is an anti-CD20 monoclonal antibody, which targets B-cells. Mepolizumab is a monoclonal antibody targeting interleukin-5, which is, in part, responsible for eosinophil differentiation [98]. Dupilumab, a monoclonal antibody to the interleukin-4 receptor, is currently being tested and

shows tremendous promise for the treatment of moderate to severe AD. Other biologics targeting interleukins 1 and 31 and receptors for interleukins 4, 13, and 33 are also being tested.

Food Allergy Testing and Allergen Avoidance

Food allergy has been documented in about a third of children with moderate to severe AD [114], with cow's milk, eggs, peanuts, and soy being the most common offenders [115]. Sensitization to these foods can occur through the GI tract [116] or via contact with the skin [117] and these allergens might act as contributors to the inflammatory response and triggers of disease in a limited subset of AD patients [118]. The vast majority of AD is not caused or triggered by food allergy [119] and food allergy screening of all AD patients is not indicated. While many parents are convinced that food allergy is causative for their child's AD, effective therapy of the AD reduces parental perception of food reactions and allays their concern about food allergy [119]. According to the National Institute of Allergy and Infectious Diseases (NIAID) published guidelines, children under 5 years old with moderate to severe AD should only be considered for food allergy evaluation if the child has persistent disease despite optimal therapy and/or has a history of immediate-type hypersensitivity reaction after ingestion of a certain food [120]. An allergy workup for the most common food allergens involves allergen-specific serum IgE levels and/or skin prick testing, followed by a diagnostic 2–8 week elimination diet of one or a few specific foods. Skin prick testing should be performed when the skin is not inflamed and without dermatographism to avoid false-positive reactions. If significant improvement of symptoms is documented, an oral food challenge, the gold standard test in the diagnosis of food allergy, is performed under medical supervision [120]. Once a diagnosis is made, avoidance of the food involved may lead to clinical improvement though the need for a strict diet remains controversial [118]. In general, specific serum IgE are highly unreliable for the prediction of pediatric AD [121] and diagnosis of food-induced eczema should not be made without food challenge testing [122].

Alternative Therapy

A number of alternative therapies have been investigated, including Chinese herbal therapy and dietary lipid supplements, such as evening primrose and borage oils, with conflicting results. A recent review by the Cochrane skin group concluded that there was insufficient evidence to support any of these therapies [123–125]. Similarly, the value of other modes of treatment such as biofeedback and hypnotherapy has not been adequately studied [98].

Special Considerations for Skin of Color

The general approach to treatment of AD does not vary for patients of different ethnic groups. However, it is important to keep a few considerations in mind. As mentioned above, a few studies have indicated that African-American patients may be more likely to have severe disease. Consequently, they may require maintenance therapy and alternative therapies to gain control of their disease and keep it in remission [126, 127]. In addition, erythema is a less reliable factor with which to determine the severity of disease in patients with darker skin pigmentation. As a result, these individuals may be underdiagnosed or may present with a greater degree of severity by the time they are finally diagnosed. It is extremely important to be cognizant of this phenomenon and to accurately assess the degree of disease severity so that the appropriate level of treatment is employed.

A study of the treatment practices of Southeast Asian dermatologists revealed variable levels of familiarity with diagnostic criteria. Appropriate use of moisturizers, topical corticosteroids, antibiotics, and other therapies were less than ideal [128]. A thorough knowledge of the diagnostic criteria, consistent use of moisturizers, and appropriately aggressive use of corticosteroids and systemic agents should be stressed in these populations [129]. It is also important to recognize that the majority of studies of phototherapy and systemic agents in AD were performed in predominantly Caucasian/White populations. Future research is sorely needed on the efficacy of these modalities in skin of color and different racial/ethnic populations.

Prognosis

As mentioned above, many cases of AD actually improve, with up to 40 % of children achieving remission by early adulthood [29]. However, recurrences are possible and these patients are often left with some mild features of disease, such as xerosis and pruritus, and may remain sensitive to factors such as heat, sweat, and various environmental allergens [30]. One study showed that the strongest risk factor for a poor prognosis with persistent disease was increased severity, with reports of frequent scratching [130]. Atopic sensitization and a strong family history of atopy also predicted a poorer prognosis in the same study.

Ongoing Research

Several new molecular therapies are currently under investigation and development for the treatment of AD. Potential targets include interleukin-4 and other T-helper 2 cytokines, chemokine receptor CCR3, and phosphodiesterase 4, which play a role in inflammatory cell migration [98]. Some studies

have suggested that patients with AD may be deficient in certain naturally occurring antimicrobial peptides, making them susceptible to colonization with *Staph. aureus* [54, 131]. Consequently, the development of new, synthetic compounds with similar antimicrobial activity could prevent superinfection of AD lesions and curtail exacerbations.

While some progress has been made in defining the epidemiology and clinical presentation of AD in patients with skin of color, further studies are warranted to better elucidate this disease, which affects so many people of different racial and ethnic backgrounds. Perhaps this will eventually provide greater insight into unique clinical features of disease in these groups, as well as guidance toward more effective diagnosis and treatment approaches. As mentioned above, different racial and ethnic groups are dramatically underrepresented in clinical trials, while many trials fail to even record ethnic affiliation [28]. It is clear that better representation in future clinical trials is critical to achieving a better standard of care for these patients.

Conclusion

AD is a disease that affects many individuals worldwide and the prevalence seems to be on the rise. Many racial and ethnic groups suffer from this condition, with possibly an increased predilection in the Black/African American population, as well as a greater level of severity. Its pathogenesis is multifactorial, involving both genetic and environmental elements in a complex interplay. It is important to remember that there are some unique features and patterns of disease in patients of different ethnic backgrounds and that these may provide clues to the diagnosis or in the assessment of the severity of the diagnosis. The physician should not be fooled by the papular pattern that often presents in African American patients, nor should they rely on erythema as a guide for disease severity. Further studies are needed to better elucidate the epidemiology of and devise more effective treatment strategies for AD in various racial and ethnic groups.

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Contact Dermatitis

30

Rashmi Unwala and Sharon E. Jacob

Abstract

Eczematous disorders are a common group of diseases that may significantly affect a child's quality of life. Contact dermatitis, for example, when seen in children of color may have clinical features such as minimally perceptible erythema and a greater papular component that could belie the severity of disease burden. Eighty years ago, it was recognized that children, even those under 3 years of age, were susceptible to contact sensitization. While there may be minor differences in skin structure and function between ethnic groups, there may be wider variability in relevant allergens identified among different ethnic populations because of cultural practices. Several of the most common relevant allergens in children of color worldwide are nickel, para-phenylenediamine, and fragrance. Children with atopy are more likely to have increased numbers of positive patch tests. Broader understanding of the types of contact sensitization that occur in children of color may increase early detection and institution of preventative practices.

Keywords

Pediatric • Contact allergy • Contact dermatitis • Skin of color • Allergic contact dermatitis • Allergen • Nickel • Para-phenylenediamine • Underserved population • Irritant contact dermatitis • Atopic dermatitis • Positive patch test • Sensitization • Metal allergy • Fragrance • Delayed type hypersensitivity

Abbreviations

ACD	Allergic contact dermatitis
AD	Atopic dermatitis
ICD	Irritant contact dermatitis
NACDG	North American Contact Dermatitis Group
PPT	Positive patch test
USA	United States

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Background/Introduction

Eczematous disorders in childhood can have a dramatic impact on quality of life particularly in those children who have difficult to treat disease [1]. Dermatologists have an opportunity to impact the course of a child's disease, if a concomitant contact dermatitis can be identified and avoidance instituted. Since a child's environment plays a central role in the development of contact dermatitis, the pediatric dermatologist can serve their patients best by understanding the patterns of allergen exposure in children, particularly children of color. The United States

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is experiencing a significant increase in the ethnic makeup of the country with a younger population leading the way [2]. This burgeoning population of children of color will also become our patient population and deserves to be understood for optimal treatment outcomes.

A central question of whether skin of color is structurally or functionally different in the way it expresses eczematous diseases has yet to be conclusively answered. Research suggests that there may be variability in structure and function between ethnic groups as it relates to eczematous processes [3]. Transepidermal water loss may be greater in black patients than white; however, this does not translate into differences in water content [4]. Black patients may also have increased spontaneous desquamation than white patients [4]. Studies that control for environmental factors and test patients of different ethnicities with irritants show no difference in the response across several populations [5, 6]. Itch sensation is an integral part of understanding dermatitis. Black patients may have increased itch perception which may stem from lower itch threshold, cultural differences, increased size of granules in mast cells, and complex neural processing of itch sensation [7]. Experimental sensitization studies have shown that black patients have lower rates of induced sensitization to dinitrochlorobenzene than whites [8]. Black patients have also been found to have superior barrier function when exposed to an irritating detergent and reduced levels of irritant contact dermatitis [9]. However, individual variability in irritation threshold may be more significant than any population-based difference.

While there still is great uncertainty in knowing whether there are physiologic differences in the acquisition of eczematous dermatitis, it is clear that ethnic patients suffer from a high burden of these diseases. An analysis of the leading dermatologic disorders in several racial groups of all ages across the USA revealed that three of the top five complaints among black adult patients were a form of dermatitis, while only one of the top five in Caucasian and Asian patients was a dermatitis [10]. This disproportionately high frequency of dermatitis as a chief complaint is also seen in studied children [11]. Allergic contact dermatitis (ACD) has been reported to have a greater adverse effect on the quality of life in non-Caucasians [12].

Clinical Presentation

- Heavily pigmented patients may have minimal perceptible erythema even in severe disease.
- A papular eczematous pattern may be more frequent in certain ethnic groups.
- Post-inflammatory pigment alteration may lead to overestimation of burden of disease.

There may be clinical differences in the phenotypic appearance of eczematous disorders between black and white skin. Patients with extremely heavy pigmentation may have minimal perceptible erythema, despite having histologic evidence of brisk inflammation and vasodilation [13] (Fig. 30.1). This difficulty in judging erythema can make it challenging to fully appreciate the severity of an inflammatory dermatosis [14] (Figs. 30.2, 30.3, and 30.4). Black patients have anecdotally been observed to more frequently show a papular eczema pattern [15] (Figs. 30.5 and 30.6). Distribution of dermatitis in black patients may also be different; black patients exhibit more extensor involvement than white patients, who have more flexural involvement. Post-inflammatory hyper- and hypopigmentation also affect the appearance of an eczematous disorder and may lead to overestimation of burden of disease if other markers of eczema activity (such as xerosis, itch, or lichenification) are not taken into account.

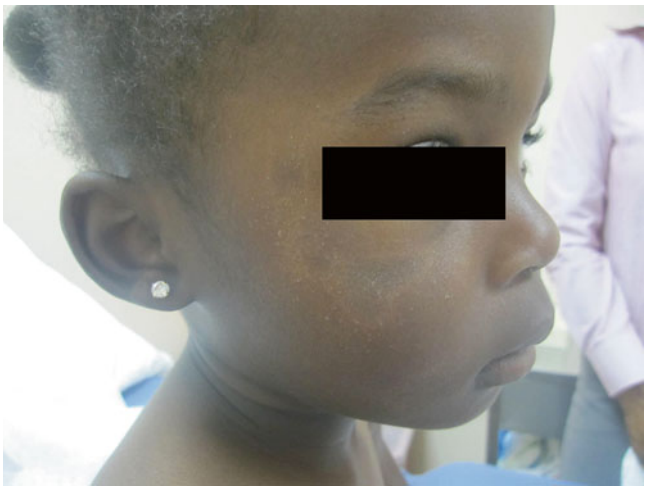

Fig. 30.1 Post-inflammatory hyperpigmentation seen in child with facial atopic dermatitis

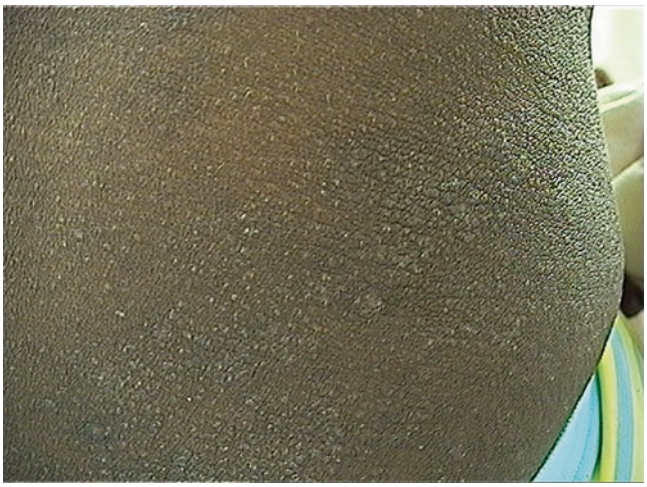

Fig. 30.2 Patchy pigmentation evident in an area of active dermatitis with no visible erythema

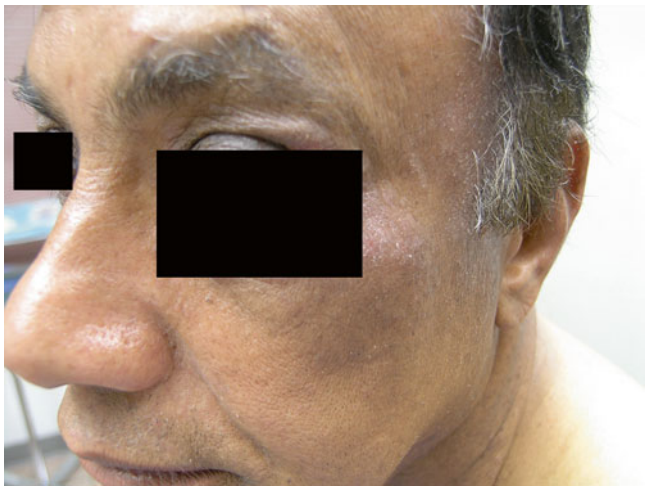

Fig. 30.3 Eyelid dermatitis with hyperpigmentation and lichenification

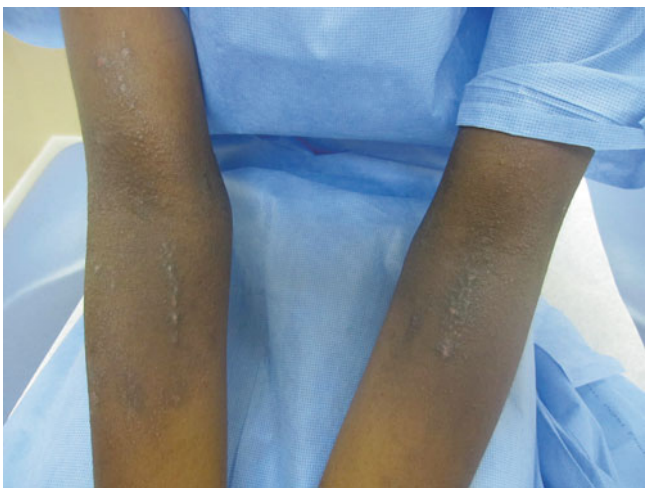

Fig. 30.4 Linear lichenification and hyperpigmentation from past flares that may lead to over-estimation of disease activity

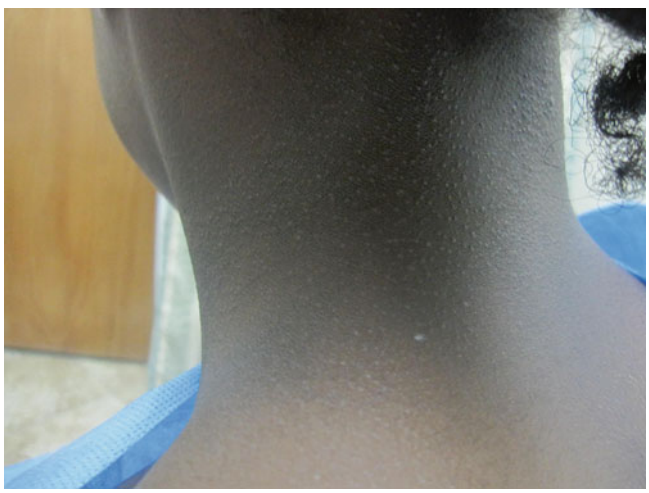

Fig. 30.5 Papular atopic dermatitis in an African-American child

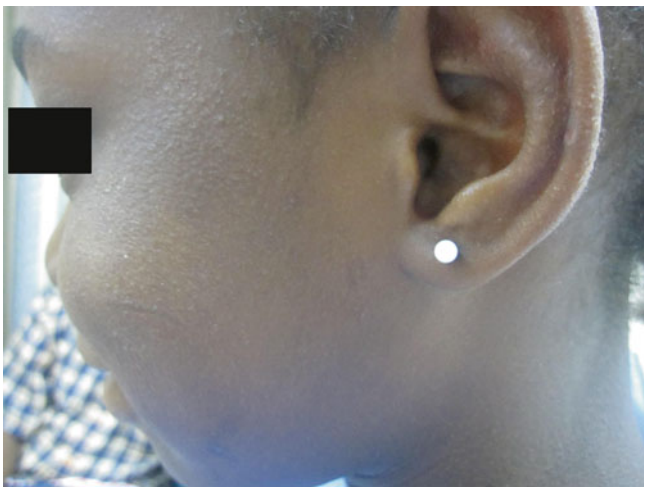

Fig. 30.6 Fine hyperpigmented papules on the face in an area of active contact dermatitis

Diagnosis/Treatment

- Allergic contact dermatitis should be suspected when there is recalcitrant or escalating dermatitis despite adequate therapy.
- The gold standard diagnostic tool is patch testing.
- Pre- and post-patch testing counseling is critical to successful management of ACD through allergen avoidance.

Once the suspicion of contact dermatitis has been raised, appropriate workup begins with a history and physical examination to determine whether the contact dermatitis is allergic or irritant in nature. About 80 % of all contact dermatitis is due to an irritant. Clues to this diagnosis are immediate onset of dermatitis within 36 h of the eliciting exposure. Depending on the concentration of the irritant, there may be erythema, scale, edema, and with exposure to extremely strong irritants, vesiculation. The dermatitis is due to direct injury of epidermal cells and subsequent release of inflammatory mediators. Patients should be educated about the importance of adequate barrier repair and avoidance of irritants.

Two other types of contact dermatitis ACD and protein contact dermatitis, PCD, account for the lion's share of the remaining 20 % of contact dermatitis. Contact urticaria, a type-I IgE mediated hypersensitivity reaction, accounts for a minority of cases. A delayed type hypersensitivity to an allergen, ACD, should be suspected when the history and physical exam suggest a pattern of dermatitis with an external causation, and when there is recalcitrant or escalating dermatitis despite adequate therapy.

In the last two decades it has become increasingly recognized that children are affected by ACD. In fact, 80 years ago, it was recognized that infants were susceptible to contact sensitization [16]. Positive patch test reactions

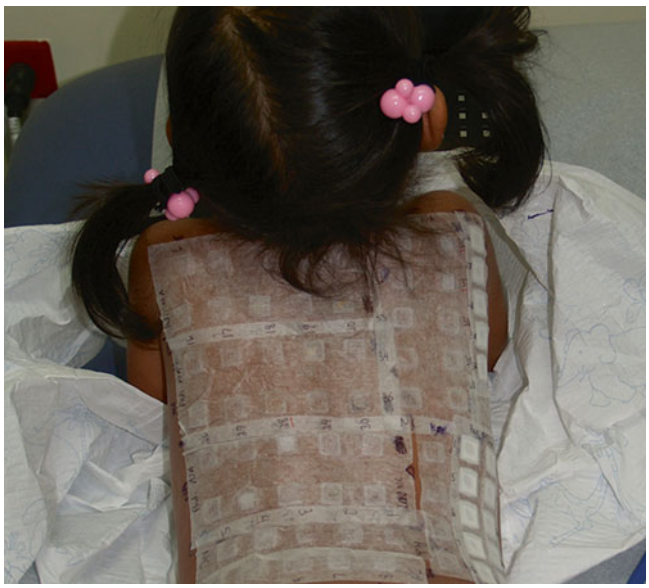

Fig. 30.7 Child undergoing patch test application to expanded series

indicative of sensitization are found across all age groups, including children under 3 years of age [17]. In the past it was thought that rates of sensitization increased with age, because numbers of exposures increased with time. More recently, however, reports have documented that younger children, particularly those under 10, have more contact sensitization [18]. Furthermore, studies from the Europe performed between 1998 and 2005 demonstrate a peak age for sensitization being in those patients 3 years and younger [19–21]. It is important to note that the prevalence of ACD in pediatric patients in the USA is especially difficult to ascertain, since large population-based studies are difficult to do in children and most affected children are not subjected to confirmatory patch testing. A meta-analysis of articles about pediatric ACD published by Simonsen et al. in 2011 showed pediatric sensitization rates of 26.6–95.6 % and relevance rates of 51.7–100 % [18].

Once a patient is suspected to have an ACD, the gold standard diagnostic tool is patch testing (Fig. 30.7). There have been several published series suggesting a standard patch test allergen series for pediatric patients. The size of the patient can limit the number of patches that can be applied and studies report testing from as few as 10 to more than 185 allergens [22–26]. Of note, there is no FDA indicated patch test device available for testing children. The T.R.U.E™ test (SmartPractice, Phoenix, Arizona) is a prepackaged, commercially available series of 35 allergens (plus 1 negative control) approved for use in adults in the USA. This has been successfully used on children in an off-label fashion, with or without supplemental allergens and in clinical trials [27–29].

Allergen series such as the American Contact Dermatitis Society [ACDS] core series, the European Standard series, and the North American Contact Dermatitis Group (NACDG) standard screening series have been developed for more comprehensive patch testing and have been used successfully in children. Use of an expanded series increases true positive detection rates when compared to the limited series available commercially. The NACDG demonstrated that 39 % of children would have had their positive relevant patch tests missed with the FDA-indicated commercially available patch test device available at the time of the study [25, 26].

Many centers that have published their data on pediatric patch testing apply standard technique to patch testing children, though some report a modified technique in pediatric patients [30–32]. Some centers decrease the concentration of some allergens (e.g. nickel, formaldehyde, fragrance mix, potassium dichromate, rubber accelerators, and cobalt) when testing infants and very young children [30]. Very intense reactions have been noted in children under 16 with para-phenylenediamine which suggests that this should be tested in a lower concentration or a decreased exposure time of 24 h as is done in Germany [33]. Many referral centers routinely update their allergen standard series to reflect changing patterns of exposure and allergens that have been found to be highly irrelevant. For example, thimerosal continued to boast high detection rates that were clinically not relevant, as the reactions associated with past exposure during childhood to vaccinations. Further, adding to the complexity of evaluating reported results is the fact that timing of patch readings is not standardized across referral centers. Pediatric patients (as is seen in adults) may have delayed positive patch test results (noted at a 7–9 day visit) to relevant allergens not identified at the earlier visits [34].

The use of supplemental allergens when testing children is just as important as when testing adults. Certain patterns of dermatitis, such as foot or flank, may call for testing with a supplemental series, such as shoe or textile. Patients with a preexisting history of atopic dermatitis may have sensitization to topical corticosteroids and some groups advocate testing children with a standard series and supplemental allergens that include corticosteroid allergy screening agents [23]. Careful history may elicit exposures to potential allergens that would be missed with only a standard series. Environmental exposures that are traditionally thought to be occupational in nature should still be considered in children based on detailed inquiry into hobbies, family businesses, and schooling. Zug et al. found that both the NACDG standard series and the two-panel T.R.U.E.™ test would have missed the supplemental allergens detected in 15.9 % of children [25].

Allergens

Children are experiencing ACD in a similar fashion to adults. And, at both ends of the age spectrum and with impairment of barrier (filaggrin mutations, ceramide reduction) an increase in ACD can be seen, which unfortunately might mimic atopic eczema or xerosis [18]. A study of NACDG data from 2000 to 2004 showed that children had similar rates and allergens of relevance (about 50 % of those tested) to adults [25]. The most common relevant allergens in the 391 children tested over a 4-year period were nickel sulfate (26.0 %), cobalt (12.4 %), neomycin (4.4 %), fragrance mix (4.1 %), gold (3.6 %), and quaternium 15 (3.6 %). Children also had higher rates of thimerosal sensitization though this was often deemed clinically irrelevant to their current dermatitis, and more associated with its use as an antiseptic and preservative in vaccines [28]. Furthermore, an analysis of six studies done at four North American patch test groups revealed a number of similarities in common with positive patch tests including nickel as the most commonly detected allergen, *Myroxylon pereirae* and other fragrances being heavily represented, neomycin, formaldehyde, and formaldehyde-releasing preservatives were also commonly detected [35].

Nickel is the most frequent allergen in children and adolescents across a vast majority of studies. Children are commonly sensitized to metals. The top three allergens identified in a series of 136 children patch tested at Mayo Clinic over a 7-year period were nickel, cobalt, and gold [24]. Note, cobalt is a commonly identified allergen that often coexists with nickel and may be considered to be a marker of nickel or metal sensitivity as it is infrequently positive in isolation.

Data on sensitization rates in various ethnic groups can be obtained from population-based studies on ACD. There are many limitations to this approach including very low numbers for smaller minority groups in the USA and lack of ability to generalize to populations outside of the study area. It is possible that an assessment of whether a child's exposure patterns seem most like the community in which they live versus the community of ethnic origin may be useful in guiding allergen selection.

A review of patch test data from 12 NACDG centers over a 6-year period compared rates of sensitization among black and white patients in the USA [36]. The patients tested reflected the ethnic distribution of the overall population, were predominantly female in both groups, and had hand, generalized, and facial dermatitis. The allergens detected were similar in both groups across the study period with minor variations, which may not reflect true differences. Black adult patients were more likely to have paraphenylenediamine sensitization during 4 of the 6 years possibly reflecting higher concentration of para-phenylenediamine in darker hair dye. White patients showed more sensitization to formaldehyde releasing preservatives, possibly reflecting a preference to creams, which require more biocides, over ointments, in contrast to preferences seen in black individuals.

Reviewing the international literature (non-US) regarding pediatric ACD, Maitz et al. [37] found that the most common allergens across the world are nickel, cobalt, fragrance, antibiotics, and rubbers. Interpretation of patch test data is influenced by choice of tested allergens, which may differ between countries. For example, Croatia has high rates of white mercury precipitate contact sensitization in pediatric patients (6.2 %), while this allergen is rarely tested in other parts of the world [38]. A meta-analysis done by Bonitsis et al. [39] in 2011 of 49 studies done on at least 100 children worldwide found that the top ten allergens, among those tested in at least two studies, were nickel sulfate, ammonium persulfate, gold sodium thiosulfate, thimerosal, toluene-2,5 diamine, palladium chloride, cobalt chloride, metallic mercury, mercuric chloride, and *p*-Aminophenol.

Racial and ethnic groups that have been reported to be affected by allergic contact dermatitis:

Caucasian, Asian, Black, Hispanic, Israeli, Indian, Turkish, Japanese, Brazilian, Singaporean, Spanish, German, Norwegian, Portuguese, English, Italian, Polish, Austrian, Finnish, Greek, French, Dutch, Swiss, Canadian, Croatian, and American [37].

Education

Pre- and post-patch testing counseling is critical to successful management of ACD through allergen avoidance. Previous experience with prick testing may lead to significant confusion on the part of the family and needle phobia from the children and delay the initiation of patch testing. Once testing has been completed, pediatric patients often have many barriers to allergen avoidance. Lengthy counseling sessions can be difficult for parents, when concomitantly caring for an uncomfortable child. The complexity of environmental control is confounded by exposures at school or during extracurricular sports [32].

Confounding Factors

What seems to be most clear when examining differences in sensitization rates across ethnic groups is that allergen exposure patterns are influenced by cultural and regional practices, not "Fitzpatrick skin type" or skin color. Skin color should not be used as a proxy for an understanding of exposure patterns in different ethnic groups. However, knowledge of the types of potentially allergenic products used by children of color can be invaluable when planning to patch test. Some cultural practices to be considered are age at first

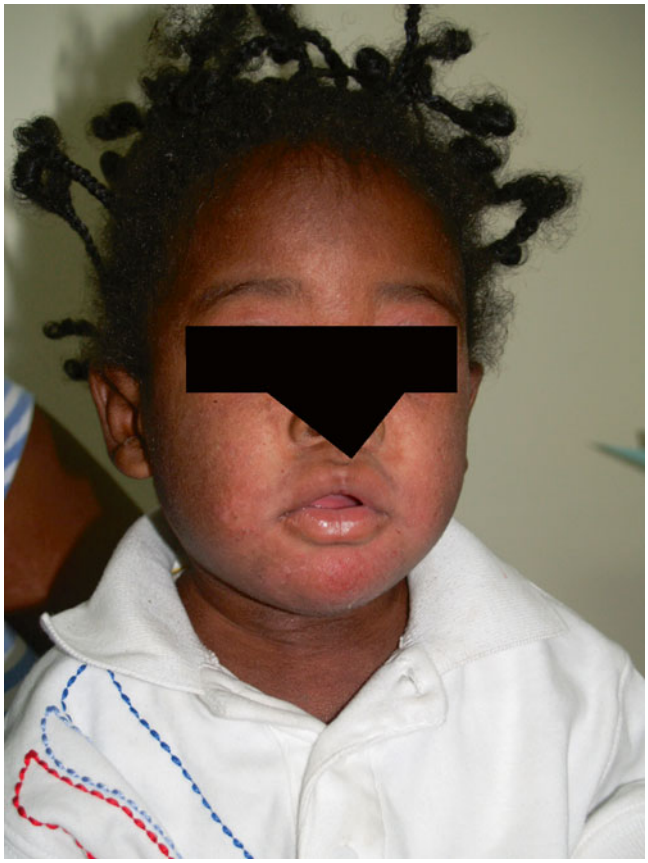

Fig. 30.8 Atopic child who was diagnosed with superimposed facial allergic contact dermatitis

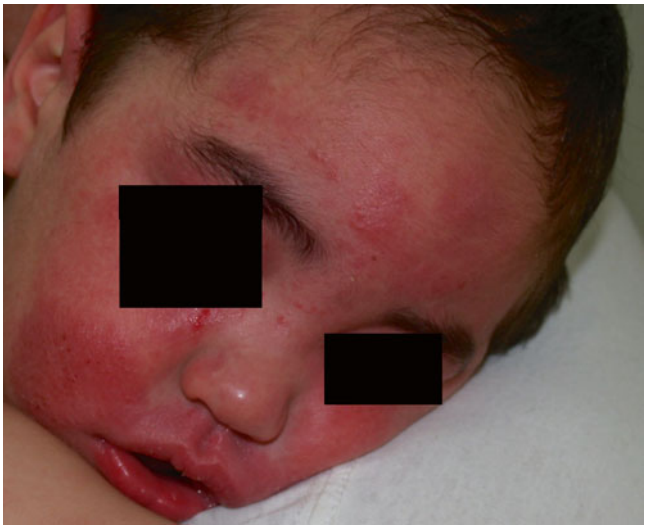

Fig. 30.9 Child with allergic contact dermatitis to formaldehyde and formaldehyde-releasing preservatives

piercing and number of piercings, use of ceremonial paints and dyes, and hair styling practices.

Children of color may also have comorbidities that could increase their potential for sensitization. Black children in the USA are more likely to have atopic eczema/dermatitis (AD) than white children [13]. Black children with AD are also six times more likely than white children to have severe disease [14]. The role of AD as a predisposing factor for ACD is controversial, as they do appear as independent phenomena and at the same time may coexist in individuals. Furthermore, clinical features of AD and ACD overlap to an extent that compromises the results of clinical studies [40].

There are an increasing number of proponents suggesting that moderate to severe AD should be an indication for patch testing due to a high rate of sensitization seen in children with high AD severity scores [28] (Figs. 30.7 and 30.8). At least 50 % of children with AD may have a positive patch test (PPT) and evidence of sensitization [22, 23, 28]. Children with AD may also have differences in PPT results from non-atopic children. In a study on 101 children using the three-panel T.R.U.E. test, the AD children had higher rates of sensitization to Balsam of Peru (20 %) and fragrance mix (19 %) [29]. Reported positive patch test results to cocamidopropyl betaine (CAPB) have been questioned as being irritant instead. That said, CAPB has been reported to be a relevant allergen in patients with atopic dermatitis [41]. Overall, the most commonly detected allergens are similar in AD and non-AD children (Fig. 30.9).

Children of color (non-Hispanic black, Hispanic, and Native American) are also more likely to be obese than white and Asian children in the USA [42]. Obesity increases occlusion and friction, which are particularly important in the pathogenesis of ACD to nickel and textiles. This may lead to an increased burden of disease in children of color who already may have significant obesity related comorbidities.

Socioeconomic status also affects the health of children of color with ACD. Unfortunately, children of color are more likely to be of low socioeconomic status than white children in the USA. Poverty, lack of insurance, under-insurance, and lack of access may compound the existing shortage of pediatric contact dermatitis experts. Children's clothing fasteners and toys may contain high levels of nickel and increase risk of sensitization [43, 44]. Allergen avoidance may be particularly difficult for patients without resources due to potentially high cost of branded alternatives. The burden of severe skin disease can be heavy on the entire family. Families with a child who has a chronic disease are impacted in many ways including economically [45]. Nearly 50 % of black children in the UK with severe AD had a parent who was unemployed, further compounding the impact the disease has on a child's life [14].

Summary/Conclusion

Recognition of some of the unique concerns for children of color with ACD can help pediatric dermatologists advocate for the health of our patients. Nickel is predominantly the most frequently detected allergen across age and ethnic

groups. Systematic nickel avoidance or directives limiting release may be a population-based method of reducing the incidence of ACD. Parents can be educated about the role clothing snaps, piercings, and belts may play in worsening dermatitis [46]. Regulation to reduce the amount of nickel in products intended for children may disproportionately help underserved groups. Education about potentially significant exposure to para-phenylenediamine through temporary henna tattoos and skin painting in childhood could be targeted to children with dark hair who may be precluded from use of para-phenylenediamine containing hair dyes as adults. These sensitized children also may be precluded from using cross-reacting systemic medications (such as sulfonamides and hydrochlorothiazide) for diabetes and hypertension [47]. Children with AD have a risk of sensitization to fragrance and resultant worsening of their dermatitis [28]. Parents can be educated about fragrance avoidance early in their child's disease and directed to use fragrance-free products preemptively.

Ideally, the pediatric dermatologist would be able to recommend a skin care regimen for children at risk for ACD that would reduce exposure to prevalent allergens while taking into account cultural preferences and cost. Cultural awareness, education, and a focus on prevention may be the best tools improving the health of children of color.

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Seborrhoeic Dermatitis in Children

31

Yee-Leng Teoh and Yong-Kwang Tay

Abstract

Seborrhoeic dermatitis is common in children and *Malassezia* species play an important role in its pathogenesis. Infants present with yellow scales on the scalp and erythematous, eczematous skin affecting the flexures. The incidence declines after one year of age. Differential diagnoses include atopic dermatitis, psoriasis, tinea capitis, candidiasis and Langerhans cell histiocytosis. Antifungal shampoos or creams, sometimes in combination with mild potency topical steroids are effective treatment.

Keywords

Pityriasis capitis • *M. furfur* • Self-limiting

Introduction

- Seborrhoeic dermatitis is common in children and affects all ethnic groups.
- *Malassezia species* play a pivotal role in the pathogenesis of seborrhoeic dermatitis.

Seborrhoeic dermatitis (SD) is a common benign condition in the paediatric population. It has been associated with other common paediatric dermatological conditions such as atopic dermatitis and psoriasis. It is rarely associated with Leiner's disease in which children have extensive SD, diarrhoea, failure to thrive, and immunodeficiency [1]. The proliferation of *Malassezia* sp. has been implicated in the pathogenesis of SD.

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Epidemiology

- Pityriasis capitis (cradle cap) is a common manifestation of SD in children especially during the first year of life.
- The incidence of SD decreases rapidly in the first few months of infancy.
- Scalp SD is a common cause for scalp scaling among prepubertal children.

In a large Australian survey on children up to 5 years of age, the incidence of SD is estimated to be about 10 % in boys and 9.5 % in girls. A population survey in a paediatric clinic in Miami showed that SD was 2.8 times more common in black children compared to white children. SD was also the sixth commonest skin condition among black children [2].

The true incidence of SD among the Asian and Hispanic children is not known.

Most children experience minimal to mild SD. Pityriasis capitis is common and occurs in 42 % of children [3]. In the paediatric age group, the highest incidence is in infants in their first 3 months of life, and the incidence rapidly declines after 1 year of age, followed by a gradual decline in children between ages 1 and 5 years. Children from as young as 2 weeks old may present with SD which tends to resolve within the first 3–4 months of life [4]. A study showed that

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SD was associated with scaling on the scalp in 54.5 % of children between ages 2 and 10 years old [5].

Clinical Features

- Infants with SD present with non-itchy greasy scales on the scalp and scaly erythematous skin in the flexures, e.g. neck, axilla and groins from the first months of life.
- Scalp SD presents as thick greasy scales on the vertex of the scalp or dandruff.
- Pruritus, which always occurs in AD patients, rarely affects patients with SD.

SD often affects the scalp, face and flexural areas in children. They often present with non-pruritic yellow scales with signs of inflammation such as erythema (Fig. 31.1). There may be overlying crusts [6]. Flexural lesions present as moist, shiny, well-demarcated scaly erythema (Fig. 31.2).

Some infants may only have scalp involvement which is also known as pityriasis capitis or "cradle cap" (Fig. 31.3). The scales can appear as white, off-white, yellow or brown, in darker children, and is usually asymptomatic in infancy, with no pruritus.

Black and Hispanic children have an increased risk of tinea capitis. It may be confused with SD if the seborrhoea-like scalp scaling is mild with minimal pruritus and kerion is not present. With a gentle pull of the hairs, the whole hair shaft and hair bulb are obtained in SD in contrast to tinea capitis where the hair shaft breaks easily. Clinicians should examine for the presence of posterior lymphadenopathy, alopecia with broken hairs and black dots as it is associated with a positive predictive value of 97 % for tinea capitis [7]. In a study done on predominantly black and Hispanic children presenting with scalp hyperkeratosis only, the patients were seven times more likely to have tinea capitis compared to SD [8]. Isolation of *Trichophyton tonsurans, Trichophyton verrucosum* and *Microsporum canis* confirms the diagnosis of tinea capitis, although other dermatophyte species may also be responsible. The use of Wood's light is useful as *Microsporum* ectothrix infections fluoresce green. Older children with scalp SD have loosely adherent, small white or grey flakes. In teenagers, SD may present dermatitis with erythema and white scaling. SD in Hispanic, Asian, and African adolescents may also present with hypopigmented scaly plaques on the eyebrow and perinasal regions [9].

Some infants who have SD in infancy develop atopic dermatitis (AD) and/or psoriasis on follow-up. The proportion of patients that develop AD varies greatly between studies, ranging from 4.5 to 37 % [6, 10–12]. It has been questioned whether SD is a variant of AD or two distinct clinical entities which may coexist. It may be clinically challenging to distinguish infantile AD from SD. However, the most obvious difference between the two conditions is the absence of itch

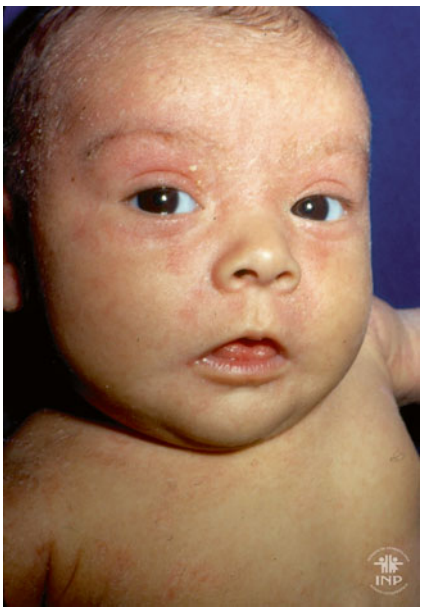

Fig. 31.1 Seborrhoeic dermatitis affecting the scalp and face, especially the eyebrows and perinasal regions (photo courtesy of Prof. Ruiz-Maldonado, MD)

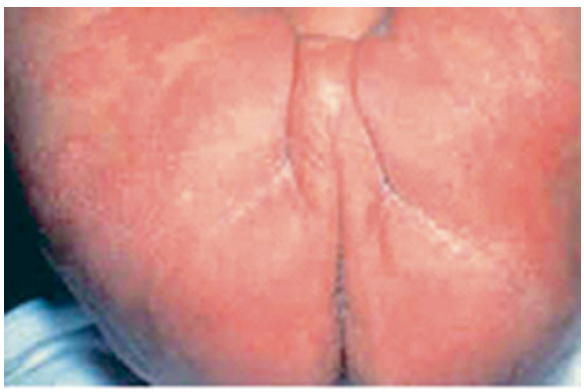

Fig. 31.2 Infantile seborrhoeic dermatitis affecting the diaper area

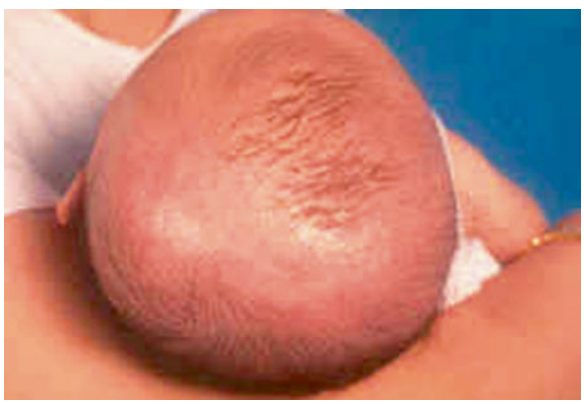

Fig. 31.3 Pityriasis capitis

in SD which is invariably present in AD patients [13]. Infantile AD may be distinguished from SD as it usually spares the diaper region which is moist, warm and occluded.

Some authors believe that infantile SD is a spectrum of clinical signs and symptoms which may be caused by infantile AD, infantile psoriasis, infantile candidiasis, Leiner's disease, and Langerhans cell histiocytosis (LCH), the latter two being rare, but of significant concern given their severity [14].

Infantile SD can be indistinguishable from infantile psoriasis especially in the "inverse" pattern which occurs in the flexures as the usual dry white scales in psoriasis is not present. Instead, the red shiny glazed psoriatic plaques appear similar to SD.

The presence of satellite lesions, papules and pustules is useful in differentiating candidiasis from SD.

Patients with LCH have seborrhoeic dermatitis-like skin lesions which are resistant to treatment. Removing gently a seborrhoea-like scalp scale, a small drop of blood will be observed, which is never present in SD (Fig. 31.4). The presence of petechiae, purpuric papules or lymphadenopathy within the areas of dermatitis should suggest the possibility of LCH [15]. Furthermore, LCH does not clear with conservative therapy. In addition, patients may exhibit unifocal or multifocal bony lumps often on the skull and facial bones. Diabetes insipidus may also be a feature if there is pituitary involvement.

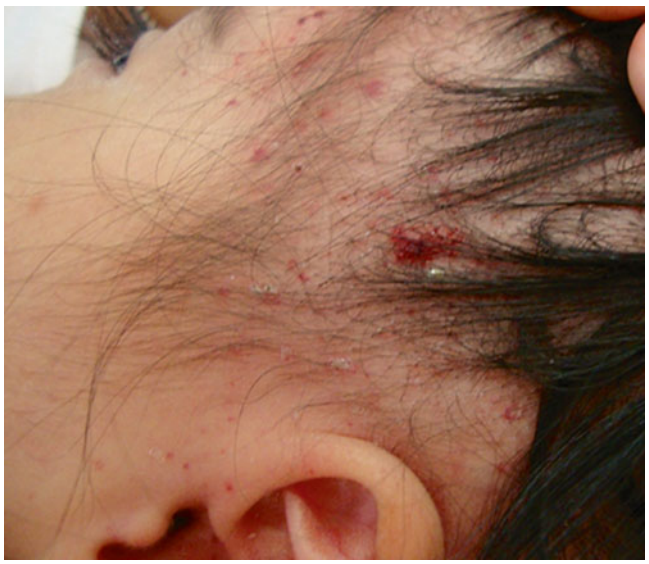

Fig. 31.4 Langerhans cell histiocytosis (photo courtesy of Dr. Carola Duran Mc. Kinster, MD)

Pathogenesis

The *Malassezia* sp. (previously known as *Pityrosporum*) is a lipophilic lipase-producing yeast [16]. The lipase splits triglycerides into fatty acids. The yeast organism ingests the saturated fatty acids, allowing the unsaturated fatty acids to penetrate the stratum corneum, causing inflammation [17]. A study of 31 Japanese adults showed that the population of genus *Malassezia* found was approximately three times more on SD skin than on non-lesional skin [18]. Studies have also shown good correlation between the *Malassezia* sp. count and severity of SD [19]. There is furthermore strong evidence of clinical response of SD to antifungal treatment in adult studies [20].

In a Chinese study carried out on adult patients with SD, *M. globosa* and *M. restricta* were found in 87.0 and 81.5 % of patients, respectively. 82.9 % of these patients also showed colonisation of two or more *Malassezia* sp. [21]. Similar results have been observed in infants with SD. A study done on Japanese infants aged 1 month showed that *M. furfur* and *M. globosa* were isolated from affected patients at significantly higher rates than from healthy infants [22].

Other studies have shown that *M. furfur* (previously known as *P. ovale* or *P. orbiculae* in the oval and round forms, respectively) has been isolated more frequently in infants with SD compared to controls [23]. Prolonged stay in the intensive care unit, parenteral nutrition, insertion of central lines in neonates are risk factors for colonisation of the infant skin with *M. furfur* [24, 25].

Infants with active SD have been found to have significant levels of a rare essential fatty acid 20:2w6. It is postulated that there is transient abnormal function of the enzyme delta-6-desaturase causing the elevated levels of 20:2w6. The normalisation of the high essential fatty acid levels correlated with a resolution of their SD [26].

Treatment

- Most infants recover without treatment
- Antifungal creams or shampoos with sometimes in combination with mild potency topical steroids are effective treatment for SD
- Patients may require re-treatment as SD commonly recurs.

Most infants will not require any treatment due to the self-limiting nature of SD. Thick scales can be softened through the application of a sterile mineral oil to the scale which is massaged into the scalp for 5–10 min before washing the hair. In a cohort study on 34 children aged between 1 month and 10 years, 97 % of patients treated with bifonazole shampoo 1 % three times weekly for 4 weeks had good to complete

Table 31.1 Management of seborrhoeic dermatitis

Site	Treatment
Scalp	• For infants, spontaneous resolution occurs within first few months. If pityriasis capitis is not resolving, trial of bifonazole shampoo 1 % is safe and effective [27] • For older children, topical antifungals such as ketoconazole or coal tar shampoo are efficacious [29, 30] • If facial and scalp SD are present concurrently, the lather of the ketoconazole shampoo can be applied onto the facial SD for 10–15 min before washing off • The antifungal shampoo should be given daily for a few weeks until SD clears and then maintained two to three times a week in patients with recurrent SD • For thicker scalp scales, 2 % salicylic acid cream is useful to loosen the scales
Face	• Ketoconazole cream combined with mild potency topical steroids can be given for facial SD in children [29, 32, 33] • Pimecrolimus cream for children above the age of 2 years who are refractory to antifungals or mild potency steroid creams [32–35] • A gentle skin cleanser is essential in inflamed facial SD
Neck and flexures	• Ketoconazole cream or selenium sulphide suspension is effective in eradicating the *Malassezia* colonisation that causes SD • They may be combined with mild potency topical steroid creams

resolution of their scalp SD [27]. There is a small study of 13 infants with scalp SD treated with ketoconazole shampoo for 4 weeks. During the course of the treatment, measured serum ketoconazole were undetectable and liver enzymes were not elevated, showing no evidence of significant systemic absorption of topical ketoconazole among infants [28]. Adult studies show that ketoconazole cream or shampoo for 3–4 weeks is efficacious and well tolerated in patients with SD [29, 30].

Alternatively, coal tar shampoo can be used to treat SD although coal tar use on the trunk may be limited by its odour and staining of skin and clothing. Selenium sulphide shampoo has been shown to be effective in treating SD in all regions in older children [31] but is generally not used for application to the face. Older children with thicker scalp scales may also benefit from salicylic acid 2 % cream for 2–3 h before shower. From the authors' experience, the use of mild topical steroids such as hydrocortisone 1 % cream combined with topical antifungals (e.g. Daktacort®) can help to reduce the erythema associated with SD. Other options include application of desonide lotion in the morning and topical antifungals in the evenings.

For patients of Black or African American descent, it may be difficult to shampoo more frequently than once a week due to intrinsic dryness of the hair shaft. In these patients, usage of pomades with selenium sulphide and/or oil-based mid-potency topical corticosteroids (e.g. fluocinolone) may be less damaging to the hair shaft (Table 31.1).

Prognosis

The prognosis in infants is generally good as SD resolves on its own. For adolescents, a course of ketoconazole shampoo and cream for scalp and facial SD, respectively, often leads to excellent clinical improvement. Studies also show that the recurrence rate of SD in adults 3–4 months post-antifungal treatment is similar to those treated with topical steroids [29, 32, 33]. Although no formal studies have been done in adolescents, recurrence is not uncommon and patients will benefit from a repeat course of treatment.

In view of the diagnostic challenge in differentiating infantile SD from other chronic conditions such as AD and psoriasis, clinicians must always consider these possible differential diagnoses in patients who do not improve with standard treatment.

Ongoing Research

There has been recent research on the use of topical pimecrolimus and tacrolimus for facial and truncal SD. Topical calcineurin inhibitors were found to be as effective as topical steroids and antifungals in adults [32–35]. A small study also showed that the pimecrolimus group were associated with fewer and less severe relapses compared to topical steroids [35]. Patients on pimecrolimus tend to have more side effects than those treated with topical steroids. Mild transient burning sensation and skin irritation were reported in 10–45 % of patients on pimecrolimus and 0.1 % tacrolimus ointment which usually subsides within the first 72 h [36–40]. Due to the transient side effects, patients often do not discontinue treatment but they should be advised of these adverse effects especially as SD often affects the eyebrows and forehead. Rosaceiform dermatitis is also a rare side effect of pimecrolimus cream which has been reported in the literature [41]. Tacrolimus may cause acne formation if used on facial locations in acne prone pre-teens and teenagers. Furthermore, these agents bear a black box warning in the United States stating that they may be associated with cancer and should not be used in children under the age of 2 years.

There is a case report of SD successfully treated with topical pimecrolimus after treatment failure treatment with topical antifungals and corticosteroids [42].

As pimecrolimus does not cause skin atrophy and with a good safety profile in children with AD [43–45], it is an alternative for patients who have clinical skin atrophy from chronic topical corticosteroids use or the minority of patients who fail to respond to antifungals or corticosteroids or have recurrent facial SD.

Conclusion

Seborrhoeic dermatitis in infants often causes distress and anxiety to parents. Parents need to be reassured that SD usually resolves spontaneously within a few months. In children, treatment with topical antifungals combined with low potency steroids is effective and safe.

SD usually resolves within a few weeks of treatment. In the presence of scalp seborrhoea and scaling, tinea capitis is an important differential diagnosis among the Hispanic and black children. In the event that the patient is refractory to standard treatment, other diagnoses such as AD, psoriasis, candidiasis, and LCH should be considered.

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Lichen Planus in Children

32

Shan-Xian Lee and Yong-Kwang Tay

Abstract

Lichen planus is a distinctive dermatosis which can affect the skin, mucous membranes, nails and scalp. The exact cause of this disease is still unknown. Lichen planus is rare in the pediatric age group, but tends to occur more frequently in children of color. It is characterised by the presence of cutaneous lesions that demonstrate the five Ps: pruritic, polygonal, purplish and plane papules. Mucosal and nail involvement is much less common in children compared to adults. There are many variants of lichen planus, with the eruptive, hypertrophic and linear variants being the most common presentations in children of color after the classical form. Diagnosis is usually made clinically, but histology and direct immunofluorescence studies can aid in difficult cases. Graft-versus-host disease, lichenoid drug eruptions and other papulosquamous disorders should be considered in the differential diagnosis. The treatment of choice for cutaneous lichen planus in children is moderately potent to potent topical corticosteroids. Most children have a good prognosis.

Keywords

Lichen planus • Children of color

Introduction

Lichen planus (LP) (from the Greek word *leichen* meaning 'tree moss' and the Latin word *planus* meaning 'flat') was first described by Erasmus Wilson in 1869. It is an idiopathic and distinctive mucocutaneous disorder that is characterised by the presence of pruritic and violaceous papules.

Epidemiology

- LP is rare in the pediatric age group.
- There is a higher incidence of LP in children of color, such as Indians and African-Americans.
- There is no gender predilection in childhood LP.

LP is seen most commonly in middle-aged adults, and is considered to be rare in children. In general, only 1 to 4 % of patients are children [1, 2].

This disorder appears to be more common amongst children from the Indian subcontinent. Most of the case series which have been published thus far have originated from India [3, 4]. Even in studies from European countries, a significant proportion of patients were of Indian origin [5, 6].

Recently, a higher incidence of LP in African-American children was also observed in a U.S. study [7].

LP is rare in infants, with the youngest documented case being 3 months old [8]. The age of onset has varied from 5 months to 14 years in previous major published studies [1, 4, 9–11].

Most studies have shown a fairly equal gender distribution, including the largest case series so far reviewing 316 cases over a 15 year period [4].

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Aetiology

The exact aetiology of LP is as yet unknown, but current available evidence points towards a cell-mediated autoimmune response.

Although LP is usually sporadic, some patients are genetically predisposed to the condition. An autosomal dominant mode of inheritance with variable penetrance has been suggested, and links between familial LP and certain human leukocyte antigen (HLA) types, namely HLA-B7 and HLA-DR10, have been found [12]. The rates of familial LP have been estimated to be about 1 to 4.3 % in previous case series [1, 13]. Familial disease is said to have an earlier age of onset, more severe and widespread involvement, and a poorer prognosis [14]. Familial LP patients are also more likely to develop certain variants of LP such as the erosive, hypertrophic and linear forms.

Several cases of pediatric LP have been described after hepatitis B vaccination [3, 15, 16]. Although LP is associated with hepatitis C infection in adults [17], this association has not been noted in children [3, 18].

Clinical Presentation

- LP can affect the skin, mucosal surfaces, nails and scalp.
- The classic form of LP is the most common presentation in children of color, in which patients present with pruritic, polygonal, purplish and plane papules primarily affecting the flexural aspects of the limbs.
- There are many variants of LP, with the eruptive, hypertrophic and linear forms being the most commonly observed in children of color.

LP has a very heterogeneous presentation, and can affect the skin, mucous membranes, nails and scalp. Table 32.1 shows the major published studies of LP in children of color.

In the classic form of cutaneous LP, patients often complain of moderate to severe itch. This is the form that affects the overwhelming majority of children [3, 4]. The flexural aspects of the limbs are the most commonly affected sites. Individual lesions are polygonal, shiny, violaceous and flat-topped papules, and may be grouped together to form plaques (Figs. 32.1 and 32.2). Small delicate white streaks forming a network over the surface of these lesions, called Wickham's striae, may also be seen. LP is a condition that demonstrates the Koebner phenomenon, whereby new lesions can appear on lines of trauma.

Mucosal involvement in childhood LP is much less common than the 60 to 70 % incidence in adults [7, 9, 11, 19]. Previous case series have reported rates ranging between 4 and 39 % [1, 2]. All mucosal surfaces including the respiratory tract, gastrointestinal tract and genitalia can potentially be affected. Oral LP is subdivided into the following types: reticular, atrophic, bullous and erosive [20]. The reticular form is the most common type, and usually presents with painless white keratotic lesions with Wickham's striae on the buccal mucosae bilaterally (Fig. 32.3). Less commonly, lesions may be found on the palate, tongue and lips [21]. On the other hand, atrophic, bullous and erosive type lesions cause burning sensations and pain. The atrophic form causes atrophic changes with erythema of the oral mucosa, while the bullous form manifests as fluid-filled vesicles and/or bullae. Erosive LP can result in painful ulcerated areas that may be complicated by secondary infection and scarring.

Nail involvement occurs in up to 10 % of adult patients with LP, but is less common in the pediatric age group. Most prior studies have reported rates varying from 0 to 9 % [1, 7, 9–11, 13, 19]. However, more recent studies have found a higher incidence of nail LP in children (13.9 and 19 %) [3, 4]. Concomitant cutaneous or mucosal LP may not be present, and biopsy of the nail matrix is sometimes required to confirm the diagnosis [22]. In a major study on pediatric nail LP, Tosti et al. classified nail LP into three categories: typical nail LP, trachyonychia and idiopathic nail atrophy [23]. Typical nail LP can present in various ways: irregular longitudinal ridging and grooving of the nail plate, thinning of the nail plate, splitting or nicking of the nail margin, pterygium formation, onycholysis, subungual hyperkeratosis and red or brown discoloration. Trachyonychia is also called twenty-nail dystrophy, in which all nails are affected and show ridging and/or pitting, lack of lustre, splitting and roughening likened to sandpaper [24]. Idiopathic nail atrophy is seen only in children and refers to the rapid and diffuse destruction of nails over a few months [23].

Scalp LP is also known as follicular LP or lichen planopilaris. Keratotic plugs surrounded by violaceous erythema are seen on the scalp in this condition, and if untreated, can lead to scarring alopecia (Fig. 32.4) [1, 9].

Although LP is classically considered to be a papulosquamous eruption, there are many different variants. These include the actinic, annular, atrophic, bullous, erosive or ulcerative, eruptive, hypertrophic, linear and pigmented forms (Table 32.2). The eruptive, hypertrophic and linear types are the most common variants in children of color [3, 4]. Actinic LP and pigmented LP are more commonly seen in tropical countries such as India, possibly due to greater ultraviolet radiation exposure [6, 11, 13]. Another notable variant of LP is an entity termed lichen planus pemphigoides (LPP). This is a rare autoimmune condition in which patients have antibodies to type XVII collagen/bullous

Table 32.1 Major published studies of LP in children of color

Number	Author; year; place	Number of patients	Years of study	Ethnicity	Age range at recruitment (years)	M:F	Morphology of lesions (%)	Oral mucosal involvement (%)	Nail involvement (%)	Scalp involvement (%)
1	Kanwar et al. [9]; 1991; India	17	1.5	Indian	8 months to 12 years	1.1:1	Classic (76), hypertrophic (12), eruptive (5.9)	5.9	5.9	11.8
2	Kumar et al. [2]; 1993; India	25	3	Indian	3–14	1.4:1	Classic (61), linear (14)	4	4	–
3	Sharma et al. [10]; 1999; India	50	3	Indian	7 months to 14 years	2:1	Classic (60), hypertrophic (26), linear (8), eruptive (4), annular (2), actinic (2)	30	–	–
4	Nanda et al. [1]; 2001; Kuwait	23	7	Kuwaiti 57 %, Bedouin 22 %, Egyptian 9 %, Saudi/ Iraqi/Indian 4 % each	2.5–12	1.1:1	Classic (70), eruptive (13), linear (9), pigmented (4), actinic (4)	39	–	9
5	Handa et al. [11]; 2002; India	87	12.5	Indian	8 months to 12 years	1.1:1	Classic (60.9), actinic (11.5), hypertrophic (9.2), linear (9.2), eruptive (6.9), planopilaris (3.5), atrophic (1.1), bullous (1.1)	13.8	2.9	–
6	Luis-Montoya et al. [19]; 2005; Mexico	24	22.5	Mexican	3–15	1:1.2	Classic (43.5), linear (30.4), pigmented (13), actinic (4.3)	4.2	8.7	–
7	Nnoruka et al. [18]; 2007; Nigeria	13	4	African	3–15	1.5:1	Classic (61.5), hypertrophic (23.1), linear (15.4), eruptive (15.4)	23.1	7.7	–
8	Balasubramaniam et al. [6]; 2008; UK	26	11	Indian 80.8 %, Caucasian 15.4 %, Afro-Caribbean 3.8 %	3–16	1.6:1	Classic (84.6), linear (19.2), hypertrophic (7.7)	15.4	3.8	–
9	Kanwar et al. [3]; 2009; India	100	7.5	Indian	2–18	1.5:1	Classic (42), eruptive (19), linear (12), hypertrophic (8), actinic (5), pigmented (2), bullous (1)	17	19	–
10	Walton et al. [7]; 2010; USA	36	18	African-American 72 %, Caucasian 13.9 %, Hispanic 8.3 %, East Indian 2.6 %	4–18	1:2	Classic (67), hypertrophic (19), atrophic (8), linear (8), bullous (5.6), pigmented (2.8)	22	–	2.8
11	Pandhi et al. [4]; 2012; India	316	14.5	Indian	2–14	1.1:1	Classic (53.8), eruptive (16.5), hypertrophic (8.2), linear (6.9)	18	13.9	8.2

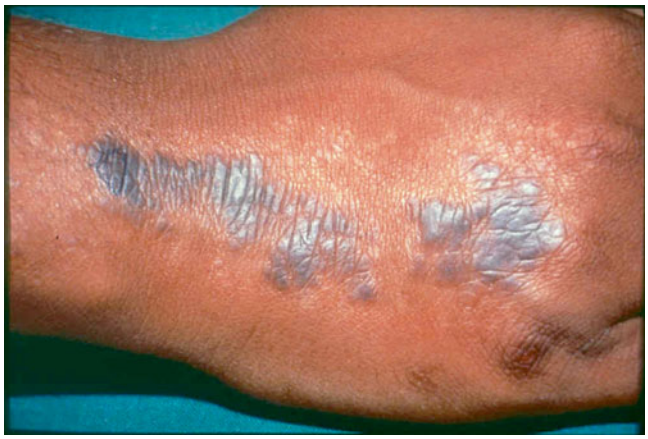

Fig. 32.1 Typical lichen planus lesions on the dorsal aspect of a patient's wrist and hand

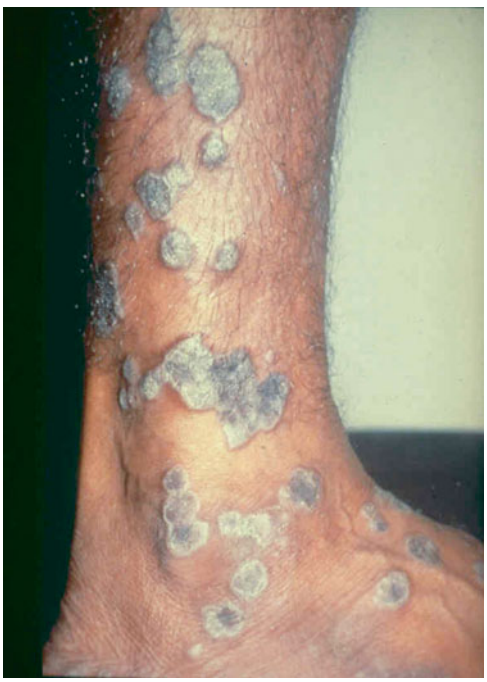

Fig. 32.2 Hypertrophic lichen planus lesions on a patient's lower limb

pemphigoid 180 antigen. While bullous LP is characterised by blister formation on pre-existing LP lesions, LPP is marked by the development of bullae on both lesional and normal skin [25–27]. Occasionally, LP can occur with other conditions and features of both disorders are present concurrently. Some examples include the lichen planus-lupus erythematosus and lichen planus-lichen sclerosus overlap syndromes [28, 29]. Lesions prominent in sun-exposed areas merit lupus screening.

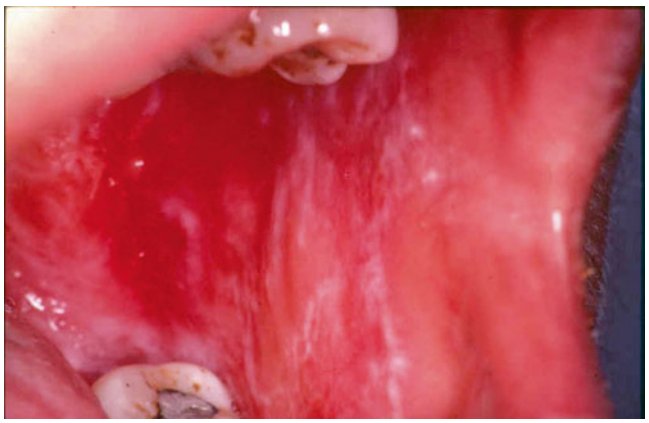

Fig. 32.3 Mucosal lichen planus with Wickham's striae involving the buccal mucosa

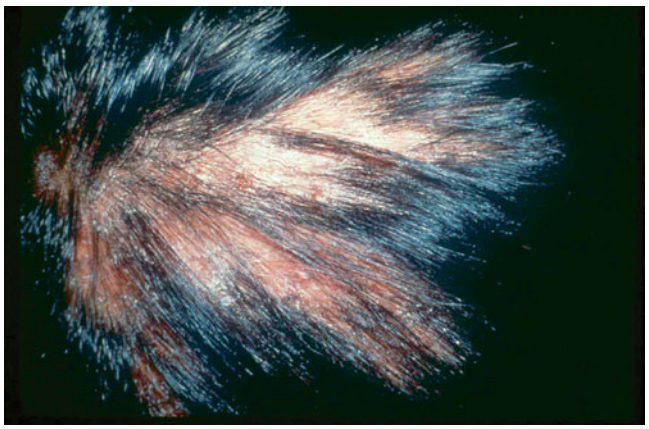

Fig. 32.4 Scarring alopecia as a result of lichen planopilaris

Diagnosis

LP is usually diagnosed clinically.

When in doubt, histopathologic examination of a representative cutaneous lesion can help to confirm the diagnosis. The classical histological appearance is that of a lichenoid reaction pattern, with vacuolar degeneration of the basal layer of the epidermis and a band-like predominantly lymphocytic infiltrate in the superficial dermis. There is also irregular epidermal hyperplasia forming a characteristic saw-tooth appearance, as well as wedge-shaped hypergranulosis [30].

Direct immunofluorescence studies of lesional skin can further aid diagnosis. These reveal fibrin deposition at the basement membrane zone and clusters of colloid bodies with immunoglobulin M (less commonly other immunoglobulin classes) and complement 3 in most patients [31].

The differential diagnosis of classical cutaneous LP includes graft-versus-host disease, lichen nitidus, tinea

Table 32.2 Variants of lichen planus

Variant	Characteristics
Actinic	This presents as well-defined bluish-brown macules, patches or papules affecting sun-exposed surfaces, often with an annular configuration. Most cases occur in children and young adults, and have been reported from Africa, India, Italy and the Middle East.
Annular	Annular LP usually occurs on the trunk and penis, and can be scattered amongst typical LP lesions. It is distinguished by a ring-like configuration of typical LP papules with a clear or slightly atrophic center.
Atrophic	This variant could represent a resolving phase of LP, in which plaques demonstrate a central depression.
Bullous	Bullae develop within existing LP lesions.
Erosive/ulcerative	Painful erosions and ulcers develop on the surface of LP lesions, most commonly affecting the palms and soles.
Eruptive	Eruptive LP is typified by the rapid development of an intensely pruritic lichenoid eruption which can become generalised.
Hypertrophic	Hyperkeratotic papules and plaques are found especially on the legs and dorsal aspects of the feet. The lesions are usually very pruritic and tend to be persistent.
Linear	Typical LP lesions are arranged in a linear pattern on the limbs, or less commonly on the trunk. Distribution along the lines of Blaschko is also possible, which reflects somatic mosaicism.
Pigmented (lichen planus pigmentosus)	This rare variant is characterised by hyperpigmented macules and papules in sun-exposed areas as well as flexural surfaces.

LP lichen planus

corporis, lichenoid drug eruptions (LDE) as well as other papulosquamous disorders such as pityriasis rosea, syphilis and plaque or guttate psoriasis. Hypertrophic LP can be mistaken for lichen simplex chronicus, and oral LP may be confused with leukoplakia or candidiasis.

LDE are an important differential diagnosis which should be considered in the appropriate context [32, 33]. Many drugs can produce a rash resembling LP. Some commonly implicated agents which may be used in children include non-steroidal anti-inflammatory drugs, anticonvulsants such as carbamazepine and phenytoin, tetracyclines, antihypertensives such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and diuretics, as well as antimalarials such as hydroxychloroquine. The latency period with LDE is usually very long, typically occurring several months to even years after initiation of a medication. LDE are more frequently photodistributed, and tend to spare the flexural aspects of the wrists as well as the mucous membranes. Individual lesions have a tendency to appear more eczematous, pityriasis rosea-like or psoriasiform compared to typical LP lesions, and Wickham's striae are less commonly seen. The histologic picture can be similar to LP, but what is suggestive of LDE is the presence of more eosinophils. Treatment is avoidance of the causative drug, but time to clearance after stopping the medication can also be prolonged, sometimes even up to several months.

Treatment

- Moderately potent to potent topical corticosteroids, as well as topical calcineurin inhibitors, can be used to treat limited cutaneous LP in children.
- Tailing courses of oral corticosteroids can be added on in cases of widespread involvement and/or eruptive disease, as well as in certain subtypes of LP that result in significant patient morbidity.
- Apart from corticosteroids, current available evidence points towards oral retinoids and dapsone as the next best treatment options in recalcitrant pediatric LP.

The mainstay of treatment for localised cutaneous LP in pediatric patients is still moderately potent to potent (class I–IV) topical corticosteroids (e.g. clobetasol propionate, betamethasone dipropionate) [34]. The main concern with regards to its usage in more extensive disease is the possibility of systemic absorption. In this aspect, topical calcineurin inhibitors such as tacrolimus 0.03 % ointment may be a good alternative option. Topical tacrolimus (0.03 %) has also been found to be effective in cases of limited cutaneous LP that are recalcitrant to topical steroids [35].

Mucous membrane lesions should be treated if the patient is symptomatic. Topicals such as corticosteroids (e.g. triamcinolone acetonide) [36], tacrolimus 0.03 % ointment [37] and viscous lignocaine are possible treatment options.

The use of topical steroids on mucosal surfaces in young children must be monitored closely, as there is a potential risk of systemic absorption. Oral corticosteroids (for instance, at a dose of 0.5–1.0 mg/kg/day as a tapering course over 3 to 6 weeks) can be added on to topical therapy if the child is very symptomatic.

For LP involving only a few nails, potent topical steroids, with or without occlusion, can be applied to the periungual folds [23]. Topical 0.05 % tazarotene gel used once to twice a day under occlusion has also been tried, but seems to yield better results when combined with a high potency steroid [3]. In older children, intralesional triamcinolone can be injected into the nail matrix of affected nails. If multiple nails are involved, however, systemic corticosteroids [5] or oral retinoids [38] are used. Oral prednisolone (0.5–1.0 mg/kg/day) can be administered as a tapering dose over 4 to 12 weeks [5]. Alternatively, mini pulses of oral dexamethasone 2.5 mg/day can be used on two consecutive days every week [3].

Systemic corticosteroids can also be combined with topical treatment in the following additional situations: widespread involvement, eruptive lesions, and subtypes of LP associated with significant morbidity, such as lichen planopilaris resulting in scarring alopecia, bullous LP and unresponsive hypertrophic LP. These are usually prescribed at a dose of 0.5–1.0 mg/kg/day as a slow taper over a 2 to 12 weeks period [1, 9, 10, 19, 39].

When traditional forms of treatment fail, oral retinoids (e.g. acitretin 0.5 mg/kg/day was used for 12 weeks in a 9 year old boy with acute extensive eruptive LP) [40] and griseofulvin for a mean duration of 13 ± 3.1 weeks [18, 19] have been used in difficult pediatric LP cases. Ultraviolet B phototherapy (e.g. 3 times a week for a period of 4 to 6 weeks) has been found to be relatively safe and effective in children with acute widespread LP [1], whereas dapsone (e.g. 1–2 mg/kg/day for 4 to 6 months) is useful for patients with chronic and recurrent disease [1, 3, 13].

Certain treatments are preferred with regards to specific variants of LP. The cornerstone of actinic LP therapy is sun protection, together with antimalarials such as hydroxychloroquine (e.g. 200 mg daily for 3 months) and/or topical steroids [41]. Hypertrophic LP may respond to the application of class I topical steroids under occlusion or intralesional injections of triamcinolone (5–10 mg/ml) [1, 9, 10]. Recently, there were two cases of childhood lichen planus pemphigoides treated successfully with a combination of systemic glucocorticoids and dapsone, for a total duration of 10 and 19 months respectively [42].

Prognosis

The natural history of the majority of typical childhood LP cases is spontaneous resolution within 8 to 15 months. With treatment, most cases respond with improvement of lesions over a period of 1 to 6 months. The affected areas are often replaced by hyperpigmentation that may last for months to years. This post-inflammatory hyperpigmentation may be particularly marked and persistent in children of color. Lichen planopilaris and hypertrophic LP may respond less favourably to therapy. Occasionally, the disease can persist for years, but recurrence rates are generally low [1, 9, 10].

Ongoing Research

Research continues to attempt to elucidate the exact pathophysiology of LP, such that better and more targeted treatment modalities can be developed to help patients suffering from this condition.

Summary

Lichen planus is a distinctive dermatosis which can affect the skin, mucous membranes, nails and scalp. The exact cause of this disease is still unknown. Lichen planus is rare in the pediatric age group, but tends to occur more frequently in children of color. Mucosal and nail involvement is much less common in children compared to adults. There are many variants of lichen planus, with the eruptive, hypertrophic and linear variants being the most common presentations after the classical form in children of color. Graft-versus-host disease, lichenoid drug eruptions and other papulosquamous disorders should be considered in the differential diagnosis. The treatment of choice for cutaneous lichen planus is moderately potent to potent topical corticosteroids. Most children have a good prognosis.

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Pityriasis Rosea

33

Shanna Shan-Yi Ng and Yong-Kwang Tay

Abstract

Pityriasis rosea is an acute, self-limiting papulosquamous eruption, common in children and young adults. It is thought to be precipitated by a viral infection, possibly human herpesvirus 6 and 7. The distribution of the papules with fine peripheral scaling is usually over Langer's cleavage lines on the trunk and proximal limbs. Atypical variants include urticarial, purpuric, vesicular, erythema multiforme like and inverse variants. As the condition lasts 6 to 8 weeks, treatment may not be necessary. Reassurance and patient education are important. Phototherapy or natural sunlight exposure may help relieve pruritus and hasten the resolution in some patients. Subsequent attacks are uncommon, occuring in 1–3% of patients.

Keywords

Papulosquamous eruption • Acute onset • Self-limiting

Introduction

Pityriasis rosea as the name implies is a scaly red rash. It was first described by a British physician Robert Willan (1751–1812) as roseola annulata [1]. Camille Melchior Gilbert in 1860 named it exanthema pityriasis rosea [2]. It is an acute self-limiting papulosquamous condition with a 6–8-week course.

Epidemiology

- **Common in all age groups, but peak presentation is in young adults aged between 20 and 29 years**
- **Female predominance**
- **Affects all ethnic groups**

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It usually presents between the ages of 10–35 years [3–12] but a study from Singapore showed an age range of 9 months to 85 years [5]. Its presentation in infants had also been noted previously [13]. Its presentation peaks at 20–29 years [4, 5, 14]. Some studies have reported a male predominance [8, 11], but most studies show a female predominance [4, 6, 7, 10, 15–18] (Table 33.1).

Pathophysiology

As the condition is typically a self-limiting disorder, with seasonal clustering, predominance during cold or winter months [7, 9, 11, 15–17, 19], and few recurrences, it is thought to be due to an infection, usually precipitated by an upper respiratory tract infection, with long-lasting immunity [4, 8, 15]. Many infective agents have been implicated, e.g., Influenza A, H1N1 [20, 21], cytomegalovirus [22], Epstein–Barr virus [23], parvovirus B19 [24] and *Mycoplasma pneumoniae* [25]. However, prospective studies have failed to show a significant change in serological titers in acute and

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Table 33.1 Demographics and seasonal variations in previous studies

Source	Location	Population	No. of patients	Incidence	Male:female ratio	Age range	Peak age	Seasonal variation
Jacyk [6]	Nigeria	All	138	2.42/100 Dermatologic patients	1.0:1.12	18 months to 55 years	15–24 years	No variation
Messenger et al. [15]	England	All	126	Not reported	1.0:1.8	Not reported	Not reported	Higher incidence in winter months
Chuang et al. [7]	Rochester, MN	All	939	172.2/100,000 Person-years	1.0:1.76	10 months to 78 years	10–35 years	Significantly higher in colder months
Ahmed [16]	Sudan	All	81	1.09/100 Dermatologic patients	1.0:1.53	Not reported	6–30 years	Peaked in cold and dry season
Olumide [17]	Lagos	All	152	4.80/100 Dermatologic patients	1.0:1.20	91 % between 5 and 35 years	10–14 years	Peaked during early part of rainy season (March to July)
Cheong and Wong [8]	Singapore	All	214	Not reported	1.85:1.0	1–61 years	20–24 years	Higher incidence in March, April, and November
Harman et al. [4]	Eastern Anatolia	All	399	0.75/100 Dermatologic patients	1.0:1.21	87 % between 10 and 39 years	20–29 years	Peaked during spring, autumn, and winter
Nanda et al. [18]	Kuwait	Children aged 12 and below	117	1.17/100 Aged 12 and below	1.0:1.38	Not reported	Not reported	Not reported
Tay and Goh [5]	Singapore	All	368	0.65/100 Dermatologic patients	1.19:1	9 months to 82 years	20–29 years	No variation
Chuh et al. [9]	Hong Kong	All	41	Not reported	1.0:1.05	5–54 years	Mean age 25.9 years	Slightly higher incidence in colder months and months with less rainfall But noted to be insignificant
Kyriakis et al. [10]	Athens	All	479	0.95/100 Dermatologic patients	1.0:1.4	35 days to 96 years	First peak male 6–10 years Second peak male 36–40 years First peak female 21–25 years Second peak female 31–35 years	Not reported
Sharma and Srivastava [11]	India	All	200	0.25/100 Dermatologic patients	2.0:1.0	1.5–65 years	13–36 years	Higher incidence from September to December
Gunduz et al. [19]	Turkey	Pediatric	51	Not documented	1.1:1.0	Not reported	6–11 years Mean age 8 years	Peaked in winter
Ayanlowo et al. [12]	Lagos	All	427	3.7/100 Dermatologic patients	1.0:1.55	Not reported	10–29 years	Peaked in rainy season

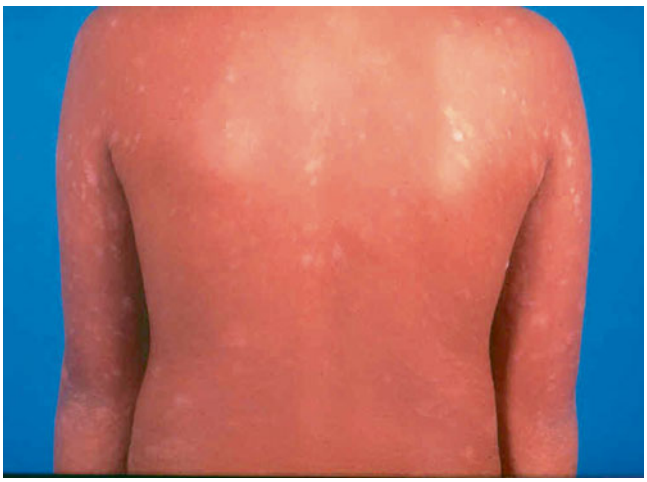

Fig. 33.1 Papules and plaques over the trunk with peripheral collerette scaling in a 'fir tree' pattern

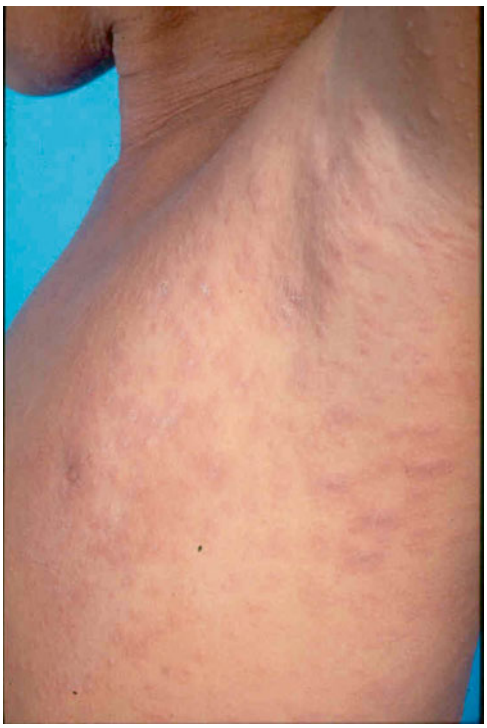

Fig. 33.2 Papules and plaques over the trunk with peripheral collerette scaling

convalescent stages for mycoplasma, cytomegalovirus, Epstein–Barr virus and parvovirus B19 [26, 27]. There are reports of the association of human herpesvirus-7 (HHV-7) with polymerase chain reaction (PCR) analysis and less so human herpesvirus-6 (HHV-6) with pityriasis rosea [28–31]. But they remain controversial [32–34].

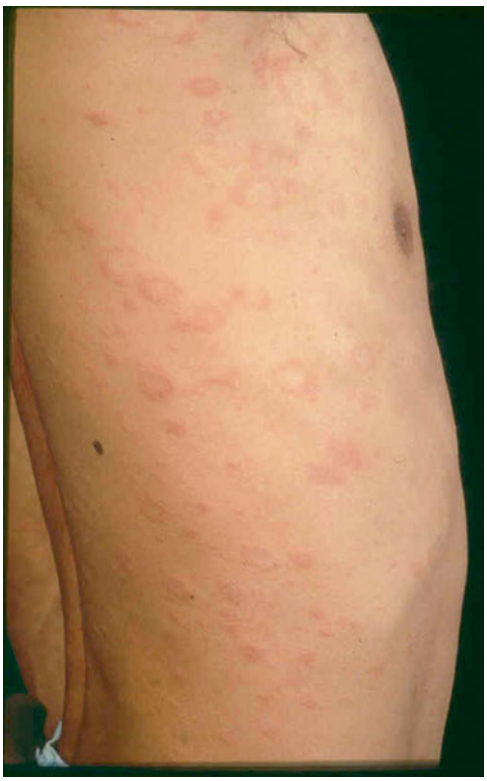

Fig. 33.3 Papules and plaques in a circumferential pattern along Langer's cleavage lines

Clinical Presentation

- **A herald patch may be present**
- **Distribution of rash is typically over Langer's cleavage lines over the trunk**
- **Atypical presentations over the scalp, face, limbs, palms, and soles can be found**

A herald patch, which is a single isolated lesion, can be found classically on the trunk but can also occur on the upper arm, neck, or thighs. The herald patch is seen in 17–94 % of cases [5, 26]. This oval patch varying from about 1 to 10 cm with collarette scaling can be mistaken for tinea corporis or eczema. Approximately 5 % of patients may feel a mild prodrome of headache, fever, malaise, or arthralgias [35]. Within a few days after the herald patch, there is a subsequent secondary eruption over the trunk and proximal extremities of lesions in a T-shirt and shorts distribution with peripheral collarette scaling (Figs. 33.1 and 33.2) which has been reported to be enhanced by epiluminescence dermatoscopy [36].

The orientation of these lesions on the posterior trunk is referred to as a "fir tree" or "Christmas tree" pattern [37]. "Langer's cleavage lines" is now proposed to be the most appropriate term with the V-shaped pattern on the upper chest and back, circumferential pattern around the shoulders and hips, and transverse pattern on the lower anterior trunk and lower back (Fig. 33.3) [38]. Atypical forms of pityriasis

Table 33.2 Treatment

Education and reassurance
Topical corticosteroids
UVB or UVA1 phototherapy
Erythromycin
Acyclovir

rosea include an inverse pattern where the face and extremities are affected more than the trunk [39]. African patients have been reported to have a more extensive rash with more frequent involvement of the face and scalp [6]. It has been reported to present in the scalp in children [40] and when presenting on the soles can mimic secondary syphilis [41]. Other atypical forms of presentation include a vesicular eruption [42], erythema multiforme-like rash [43], urticarial [44], and purpuric variants [44, 45].

Treatment

- **Symptomatic treatment includes antihistamines and topical corticosteroids**
- **Phototherapy or natural sunlight exposure may help ease pruritus and hasten resolution of rash in some patients, but there is an increased risk of post-inflammatory hyperpigmentation especially in darker skin types**
- **Erythromycin or acyclovir can be tried to hasten resolution of the rash and decrease pruritus**

As the condition is self-limiting in about 6–8 weeks, treatment may not be necessary (Table 33.2). However, pruritus can be bothersome and oral antihistamines and topical corticosteroids may be helpful. These provide symptomatic relief but do not help in the clearance of the rash [46]. Systemic steroids have not been shown to be effective [46, 47]. Exposure to UV-B therapy starting at 80 % of the minimum erythrogenic dose may relieve pruritus in as little as 24 h but may increase the incidence of post-inflammatory hyperpigmentation [48–50]. Alternatively, low-dose (10–30 J/cm^2) UV-A1 phototherapy given 2–3 times a week until resolution may be tried [51]. Early administration of erythromycin 1 g taken orally in four divided doses for adults or 25–40 mg/kg divided four times daily in children for 2 weeks in a double-blind placebo controlled trial led to early resolution of symptoms [52]. However, subsequent studies did not find erythromycin or azithromycin useful [53, 54]. There is some evidence that oral acyclovir 1 g five times a day for 7 days at the onset in adults has been shown to shorten the duration of the disease [55, 56]. Subsequently, lower dosages of acyclovir 400 mg five times a day for 1 week was shown to be equally effective [57]. Recent studies have shown that despite its effectiveness in herpes simplex virus infection, acyclovir was not as effective as ganciclovir and forcarnet against HHV-6 and 7 [58]. This is because acyclovir is thymidine kinase-dependent whereas HHV-7 lacks the thymidine kinase gene [59]. There are yet to be published data on the effectiveness of ganciclovir and forscarnet in pityriasis rosea.

Prognosis

The condition is generally self-limiting and its recurrence is reported to be between 1 and 3 % [37, 44]. It usually lasts between 6 and 8 weeks but can last up to 3–6 months [8, 37]. Darker skin individuals tend to recover with post-inflammatory hyperpigmentation [60].

Ongoing Research

As further research continues on the etiology of pityriasis rosea, the use of erythromycin, azithromycin, and acyclovir in pityriasis rosea remains controversial.

Conclusion

Pityriasis rosea is a benign condition. Reassurance and patient education are important. For atypical presentations, one will need to consider the other causes of a papulosquamous eruption such as tinea corporis, nummular eczema, guttate psoriasis, pityriasis lichenoides, secondary syphilis, and drug eruptions.

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Paediatric Psoriasis

34

Colin Kwok

Abstract

Psoriasis in the young shares a number of common features with adult psoriasis but has its unique features. Chronic plaque psoriasis remains the commonest presentation. Nail and joint involvement is rare. Topical treatment is preferred. Cultural practices influence the presentation and treatment.

Keywords

Paediatric • Psoriasis • Asia • Genetics

Epidemiology

- **Paediatric psoriasis affects every Asian country.**
- **Asian patients share many common features with Caucasian patients.**
- **Differences between Asian and Caucasian patients may be due to different genetic factors.**

Psoriasis is a genetically determined, chronic inflammatory, and proliferative disease.

It has a worldwide prevalence, affecting 1–3 % of the population and affecting every race, albeit at different rates.

Psoriasis is a clinical diagnosis. Our understanding of the disease has progressed from a purely clinical level to the molecular level.

Psoriasis affects the skin, joints, and nails.

The commonest manifestation is chronic plaque psoriasis. Clinically, plaque psoriasis presents as well-demarcated salmon-coloured plaques with silver scales (Fig. 34.1).

Histologically, there is an increase in multiplication and turnover of keratinocytes. Three key features are a thickened parakeratotic epidermis (3–5× thicker), elongated dermal papillae with dilated tortuous capillaries, and sparse inflammatory infiltrate (mainly T-lymphocytes and some neutrophils) in the papillary dermis. There may be collections of neutrophils in the epidermis known as Munro's microabscesses. These abscesses are sterile.

At the molecular level, there is a predominant Th1 lymphocyte proliferation leading to an increase in cytokines such as IL2, TNF-α, and IFN-γ.

Many studies have been published on psoriasis in the Caucasian population, much less non-Caucasian psoriasis.

This chapter concentrates on Asian paediatric psoriasis.

Asian skin [1] can be subdivided into:

(a) South Asia—Pakistan, India, Sri Lanka
(b) South-East Asia—Thailand, Malaysia, Singapore, Indonesia
(c) East Asia—Japan, Korea, China

In paediatric Asian psoriasis patients (18 years and below), the peak incidence is at around 10 years with equal sex ratio.

A family history of psoriasis is present in about one-third of the cases. If one parent has psoriasis, there is a likelihood of 30 % that his or her child will have psoriasis. The risk goes up to 65 % with both parents involved [2].

Certain susceptibility genes have been mapped (Table 34.1).

PSOR1 (psoriasis susceptibility 1) is the major gene determining the risk of psoriasis. It is located on the MHC site on chromosome 6, with the *HLA-Cw6* allele imparting risk in both Caucasians and Asians.

In Han Chinese, HLA-Cw6 is found to be associated with susceptibility to psoriasis [3]. HLA-Cw6-positive patients

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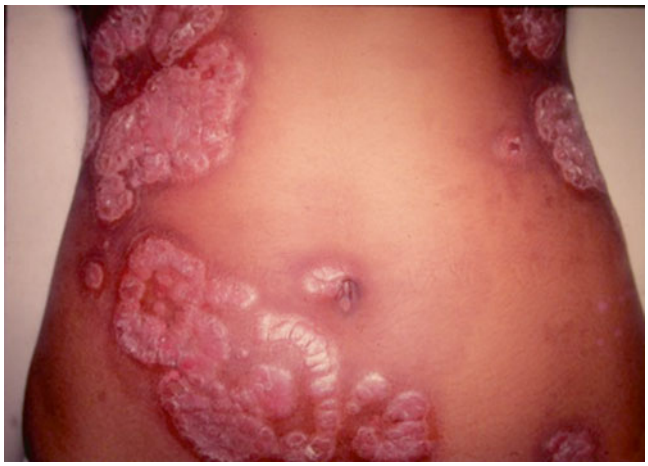

Fig. 34.1 Well-defined *salmon-coloured* plaques, topped with *silvery* scales in chronic plaque psoriasis

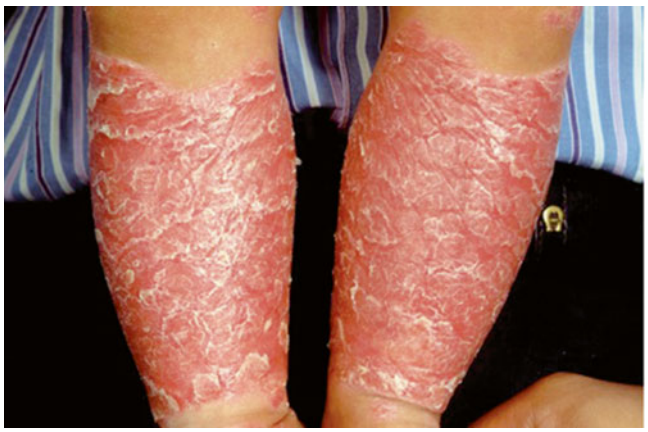

Fig. 34.2 Psoriasis tends to symmetrically affect the extensor aspect of the limbs

Table 34.1 Susceptibility genes in psoriasis

Genes	Chromosome
Psors 1	6q
Psors 2	17q
Psors 3	4q
Psors 4	1q
Psors 5	3q

tend to have early onset and more serious psoriasis. It also confers an increased risk of guttate psoriasis.

Thai studies have shown that *HLA-Cw1-B46* carriers have greater nail involvement, and later age at onset as compared with *HLA-Cw6* carriers [4].

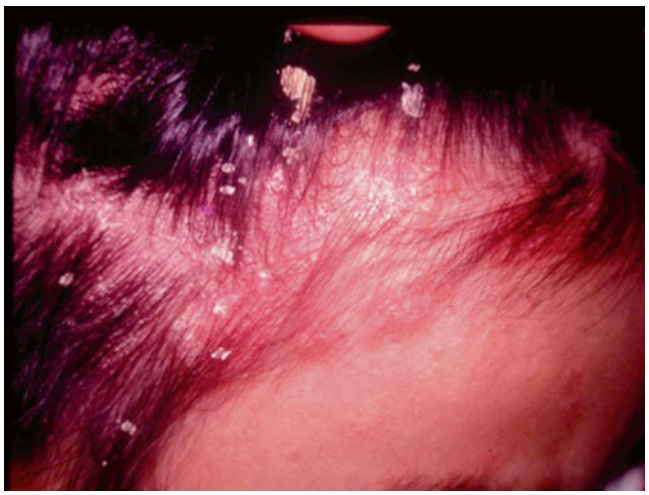

Fig. 34.3 Scalp psoriasis may be the first manifestation of psoriasis

Clinical Presentation

- **Asian paediatric psoriasis commonly presents as chronic plaques.**
- **Joint and nail involvement is less common compared to adult psoriasis.**
- **Koebner phenomenon is common and itch is milder in children.**

The commonest presentation is chronic plaques psoriasis [5–9] The lesions commonly affect the scalp, the extensor surfaces of the limbs, and trunk (Figs. 34.2 and 34.3).

Koebner phenomenon is present in 50 % and there is milder itch in children.

Nail and joint involvement is rare compared to adult psoriasis.

Data from multi-ethnic societies, e.g. Singapore, showed that Indians, compared to Malays and Chinese, tend to have a higher incidence of psoriasis [6].

A comparative trial in a multi-ethnic population in Singapore [10] (SG) against a predominantly Caucasian population in Netherlands (NL) revealed more Dutch children with an affected family member (73.3 % vs. 13.6 %). Presence of itch and triggering factors were more common among Dutch children (80 % vs. 14.2 % and 33.3 % vs. 7.4 %, respectively). Both groups shared similar triggering factors like stress and infections. Other similarities included mean age at presentation (NL group 11.3 years; SG group 14.1 years) and gender ratio (NL group, M/F 1:1.1; SG group, M/F 1:1.4). In both cohorts, plaque psoriasis was the most common type, with the head, followed by the limbs, being most involved. Similar proportions of children in both countries had nail involvement, and psoriatic arthritis was rare.

Aggravating factors include:

1. Mechanical trauma—Koebner phenomenon
2. Infection—streptococcal throat infection
3. Drugs—lithium, beta-blockers, withdrawal of systemic steroids
4. HIV infection

Table 34.2 Morphological forms of psoriasis and differential diagnoses

Types	Differentials
Chronic plaque	Discoid eczema Tinea corporis
Guttate	Pityriasis rosea Pityriasis lichenoides Secondary syphilis
Erythrodermic	Other endogenous eczema Drug eruption
Localised pustular	Candidiasis Folliculitis
Generalised pustular	Pustular drug eruption Acute generalised exanthematous pustulosis (AGEP)
Palms and soles	Hand/feet eczema Dermatophytosis
Scalp	Seborrhoeic dermatitis
Nail	Lichen planus Onychomycosis
Psoriatic arthropathy	Rheumatoid arthritis

Differential Diagnosis

Table 34.2 lists the differential diagnoses of the morphological variants of psoriasis

Psoriasis affects the nails. Nail changes include pitting (commonest change), distal onycholysis, subungual hyperkeratosis, discoloration (e.g. oil drop), and dystrophy. None of these clinical signs are pathognomonic of psoriasis.

Various forms of psoriatic arthritis are seen:

1. Oligoarthritis—This affects less than five joints asymmetrically.
2. Polyarthritis—Resembles rheumatoid arthritis
3. Distal arthritis—This affects the distal inter-phalangeal joints of the hands and feet
4. Arthritis mutilans—It is the end stage of arthritis
5. Spondyloarthropathy—Resembles ankylosing spondylitis

Management of Childhood Psoriasis

- **Topical treatment is preferred.**
- **Systemic treatment may be considered for extensive psoriasis.**
- **Patients may be on traditional medications.**

In every decade since the mid-twentieth century, there have been new therapies for psoriasis:

Pre-1950	Coal tar, broadband ultraviolet B
1950s	Corticosteroids, methotrexate
1960s	Topical retinoids
1970s	PUVA (photochemotherapy)
1980s	Retinoids (etretinate, acitretin), narrowband UVB
1990s	Cyclosporin, topical calcipotriol, and tazarotene
2000s	Topical tacrolimus, topical pimecrolimus, biologics

Management includes both specific therapy and patient/parent education so that they understand the disease and can cope better with the illness.

Education

It is important to give the right information about what psoriasis is about and what it is not about. Allow time for patients and parents to ask questions and allay fears or guilt.

Reassure the parents that psoriasis is not infectious. It is non-scarring and not influenced by diet.

The use of traditional medications is very prevalent in Asian societies. Many traditional therapies aim to balance the body system. Parents may not consider the use of certain herbal remedies, be it topical or oral, as medicine. The doctor may have to ask specifically of its use.

Treatment [11, 12]

Special consideration is given to children. A child's skin is thinner than an adult's. Assuming lifelong treatment, a child will have a longer exposure to therapeutic agents compared to adult-onset psoriasis.

Treatment should be individualised.

The three main pillars of treatment are:

Topicals: e.g. tar, steroids, dithranol, calcipotriol, calcitriol, tazarotene, emollients

Phototherapy—UVB, PUVA

Systemic therapy—methotrexate, acitretin, biologics

Topical treatment is used in limited psoriasis affecting less than 10 % of the body surface area.

For more extensive disease ((PASI > 10 or >10 % BSA), pustular or erythrodermic psoriasis, and those not responding to topical therapy, phototherapy or systemic therapy may be considered.

Topicals

Topical treatment has the advantage of a high efficacy-to-safety ratio.

It is also more convenient compared to phototherapy and systemic therapies.

The majority of psoriasis patients have mild-to-moderate psoriasis. Hence topical therapy alone is a viable treatment option. Even for severe psoriasis, topical treatment can be an adjunct to systemic therapies.

There are a number of topicals that can be used either singly or in combination.

Certain factors influence the choice of topicals:

1. Costs—In many parts of Asia, health care is not heavily subsidised by the governments. Patients may have to pay in part or full the expenses of the medication.
2. Site of body—The face, neck, and flexures are more sensitive areas. Avoid topicals that can cause irritation, e.g. calcipotriol, coal tar, and dithranol. Lotions and gels are more suitable for hair-bearing areas such as scalp. Ointments are useful for very dry skin.
3. Types of psoriasis. In pustular psoriasis, avoid topicals that can irritate the skin, e.g. coal tar, dithranol, and tazarotene.

Coal Tar

Coal tar solution in cream (LPC) is available in several concentrations: 5, 10, and 15 %.

For thick, recalcitrant plaques, stronger crude coal tar ointment, 5, 10, and 15 %, is available.

Occasionally salicylic acid 2 % can be mixed with tar, especially if the lesions are scaly.

Coal tar is inexpensive.

It, however, has an unpleasant smell and stains clothes and furniture. It may irritate the skin and can cause tar folliculitis.

Dithranol

Dithranol is available in various concentrations from 0.5 to 3 % in cream or ointment.

Like coal tar, it is inexpensive but tends to irritate the skin and stains clothing.

Start with the lowest concentrations and use short contact time of 10–60 min before washing the preparation off.

Topical Steroids

Topical steroids are cosmetically elegant, suitable for scalp, face, intertriginous regions, palms, and soles as well as inflamed psoriasis intolerant of other anti-psoriatic preparations.

It can cause cutaneous atrophy and striae. Ideally do not go beyond Class 2 steroids (e.g. 0.025 % Betamethasone valerate) for flexures and Class 3 steroids (e.g. 0.1 % Betamethasone valerate) for the body.

Vitamin D Analogues

It is commercially available as calcipotriol and calcitriol.

It is well tolerated and can be combined with topical steroids to reduce the rebound phenomenon of steroids.

The main side effect of calcipotriol is irritation; hence avoid its use on the face and flexures. Calcitriol is less irritating and may be used on the face and flexures.

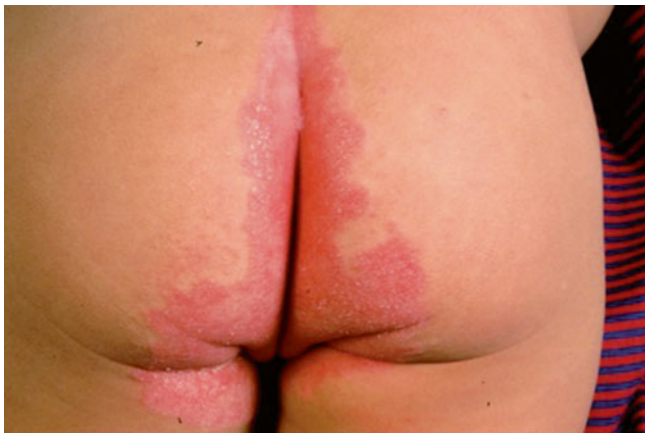

Fig. 34.4 Flexural psoriasis. It is usually not as scaly as psoriatic plaques elsewhere on the body. But the plaques retain its salmon hue and well-defined borders

Fig. 34.5 Nail involvement in psoriasis with pitting and distal onycholysis

Do not exceed 50 g/week/m^2 to prevent hypercalcemia.

A fixed combination of calcipotriol and betamethasone dipropionate, is reserved for thick, recalcitrant psoriatic plaques (Fig. 34.4).

Tazarotene

It is a vitamin A analogue that can be used for psoriatic plaques, e.g. lesions on the limbs. The main side effect is irritation (Fig. 34.5).

Phototherapy

In most dermatological centres, the more efficacious narrowband UVB (311 nm) (introduced in 1984) has replaced the traditional broadband UVB phototherapy (280–320 nm).

Systemic photochemotherapy (PUVA) is less used as it has a higher risk of skin malignancy. UVA has a deeper skin

penetration than UVB; hence hand/foot PUVA may be used for recalcitrant acral lesions.

In targeted phototherapy, a handpiece is used to direct light at specific spots on the skin. The light source may emit broad-based UVB (e.g. Muticlear® 295–315 nm) or a single wavelength (e.g. Excimer laser 308 nm). Targeted phototherapy has the advantage of delivering light only to lesions at a higher dose with consequent faster improvement and avoiding non-affected skin. It is useful for recalcitrant plaques and hard to reach areas. Targeted phototherapy is, however, labour intensive and has a higher incidence of adverse side-effects.

The adverse effects of phototherapy can be divided into acute effects, similar to sunburn (pruritus, erythema, tan) and chronic effects (photoaging, skin malignancies).

Systemic Therapy

Systemic therapy, such as methotrexate (MTX), acitretin, and cyclosporin, is used in extensive psoriasis (e.g. erythroderma) or recalcitrant psoriasis.

Screen patients for hepatitis B and C and tuberculosis.

MTX is given in a weekly oral dose of 0.3–0.5 mg/kg/week. It is available in 2.5 mg tablets. Monitor haematological and liver function. Folate (5 mg/week) improves the tolerance (side effects) of MTX.

Liver biopsy is recommended with every cumulative dose of 1.5 g. It is gradually being replaced with monitoring of serum Procollagen type III N-terminal peptide every 3–6 months (if available).

Acitretin is effective in plaque and pustular psoriasis. It is more effective when combined with phototherapy. The therapeutic dose is 0.5–0.75 mg/kg/day. Monitor liver function every 3–6 months. It is teratogenic; hence ensure patients of child-bearing age have prophylaxis against pregnancy.

Cyclosporin is used in the dose of 3–5 mg/kg/day. Check the renal function and the blood pressure with every visit. The serum creatinine should not exceed 30 % above the baseline. Cyclosporin also has a number of drug interactions (e.g. with erythromycin).

Biologics

These biological response modifiers target various molecules. There are three main classes of biologics used in psoriasis. They are given either by subcutaneous or intravenous route:

1. T-cell targeted—Alefacept (Amevive®), Efalizumab (Raptiva®—withdrawn)
2. Anti-TNF alpha—Etanercept (Enbrel®), Adalimumab (Humira®), Infliximab (Remicade®)
3. Anti IL12/23—Ustekinumab (Stelara®)

The best-studied biologics in the paediatric population is etanercept. It acts by binding to circulating TNFα.

The main worry of biologics is an increased risk of infections including tuberculosis and hepatitis.

Ongoing Research

More recently, psoriasis has been found to be associated with the metabolic syndrome (odds ratio 2) [13]. Inflammatory cytokines (e.g. TNF-α) may have a role to play in the link between psoriasis, cardiovascular disease, and the metabolic syndrome.

The National Cholesterol Education Program Adult Treatment Panel (NCEP) III (2001) criteria for metabolic syndrome require three or more of the following criteria:

- Central obesity: waist circumference ≥102 cm (male), ≥88 cm (female)
- Serum triglycerides ≥1.7 mmol/L (150 mg/dL)
- Serum high density lipoprotein <40 mg/dL (1.03 mmol/L) (male), <50 mg/dL (1.29 mmol/L) (female)
- Blood pressure ≥130/85 mmHg
- Fasting plasma glucose ≥6.1 mmol/L (110 mg/dL)

Patients may need to be referred for treatment of the metabolic syndrome.

Biologics used in the treatment of psoriasis target cytokines and have been shown to reduce the components of metabolic syndrome.

Ongoing research is needed whether one should screen a child with psoriasis for the metabolic syndrome and at what age should such screening begin.

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Drug Eruptions

35

Patricia A. Treadwell

Abstract

Drug eruptions may occur with a different incidence and varied clinical appearance in children of color. This chapter will address select eruptions in order to assist the clinician to properly diagnose, work up, and treat those eruptions. Specific features that differ in children of color include obscuring of erythema by pigmentation, presence of specific HLA types, and genetic differences in metabolism of medications.

Keywords

DRESS • Fixed drug • Erythema multiforme • Photosensitivity • Stevens–Johnson syndrome • Urticaria

Acute Urticaria

Introduction

The lesion of urticaria is a transient wheal which results from mast cell and basophil degranulation. The classic description is of a wheal and flare. Histamine and vasoactive mediator release causes vasodilatation, increased vessel permeability, and subsequent extravasation of fluid in the superficial dermis.

Epidemiology

- **No ethnic differences**
- **Urticaria are transient lesions**
- **Urticaria may be hard to appreciate in richly pigmented skin**

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There are no racial or ethnic predilections for urticaria [1]; however, in richly pigmented skin, the lesions may be challenging to diagnose (because of the difficulty appreciating the erythema). Acute urticaria in children can be triggered by infections, drug hypersensitivity, and less often food allergies. The infections implicated in acute urticaria are viral, streptococcal, and urinary tract infections. The most commonly reported drugs causing urticaria in children are antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) [2].

Clinical Presentation

- **Each lesion lasts for 24 h or less**
- **Itching is noted**
- **Annular lesions noted in "urticaria multiforme"**

Urticarial lesions can occur on any area of the body. They are raised, with well-defined edematous borders and central pallor. Each individual lesion will last for 24 h or less. Itching is a prominent feature. Urticaria on the palms and soles is characterized by swelling and erythema which can be painful. Annular urticarial lesions have been classified as "urticaria multiforme" [3]. This variant has been most often noted to be triggered by antecedent viral illnesses or antibiotics. Giant urticaria can be associated with streptococcal infection.

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Treatment

- **Avoid the offending agent**
- **Treat with second-generation H1 antihistamine**
- **Sedation and psychomotor impairment noted with first-generation H1 antihistamines**

Avoid the offending agent if possible. Pite et al. [2] recommended use of second-generation H1 antihistamines for treatment of urticaria. The authors discuss the sedation and psychomotor impairment associated with first-generation H1 antihistamines which makes them less desirable.

Prognosis

The prognosis associated with acute urticaria is generally good [4]. If they are triggered by infectious agents or foods, they tend to resolve spontaneously when the infection resolves or the food is eliminated from the digestive tract. The urticaria triggered by drugs may soon resolve when the drug is withdrawn, but can possibly persist (especially with drugs with a long half-life).

Ongoing Research

Research continues in order to delineate the best approaches to diagnosis of the triggers for urticaria in order to delineate the most efficacious treatments.

Conclusion

Urticaria can be difficult to recognize in skin of color, but being aware of the differential diagnosis for triggers can be particularly useful.

Fixed Drug Eruption

Introduction

Lesions which recur in same site in response to specific agents are known as fixed drug eruption (FDE).

Epidemiology

- **Uncommon in childhood**
- **May be underdiagnosed in children**
- **Occur in association with analgesics, antibiotics, and laxatives**

FDEs are somewhat uncommon in children, but are often underdiagnosed. The most common medications associated with FDE are analgesics (including NSAIDs), antibiotics (especially cotrimoxazole), and laxatives [5]. One study noted propranolol associated with FDE [6].

Clinical Presentation

- **Brownish or violaceous center**
- **May be bullous**
- **Typically have residual hyperpigmentation**

FDE lesions are typically oval or round fairly well-demarcated erythematous patches. The center has a brownish or violaceous color (Fig. 35.1). The lesions can be noted anywhere on the body and/or on mucosal surfaces [5]. When the lesions resolve, residual hyperpigmentation is typical. Occasionally blisters may develop within the lesion (Fig. 35.2) [7].

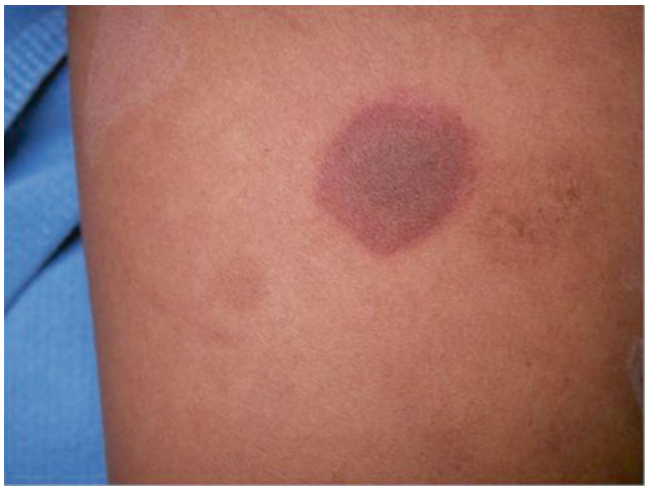

Fig. 35.1 Fixed drug eruption to ibuprofen

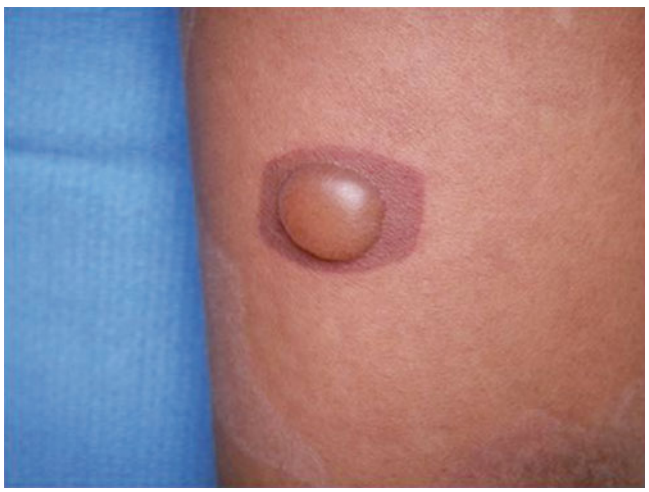

Fig. 35.2 Bullous formation in patient in Fig. 35.1

Non-pigmenting FDE (NPFDE) has only rarely been reported in children. NPFDE has similar features of FDE without the residual pigmentation [8].

Treatment

- **Avoid offending agent**
- **Drug challenge may cause relapse**

Identification and avoidance of the triggering agents assists in prevention of future lesions. Drug challenge tests can provoke relapses [8].

Prognosis

If the triggering agent is identified and avoided, the lesions can resolve. In skin of color, the postinflammatory hyperpigmentation may be particularly noticeable and may be persistent.

Ongoing Research

Ongoing studies to identify the causative agents associated with FDE will be useful in diagnosing this entity.

Conclusion

FDE is a unique category of drug eruptions with pigmentary changes as a prominent feature.

Photosensitive Drug Eruption

Introduction

Photosensitive drug eruptions occur with the combination of a sensitizing drug and ultraviolet (UV) exposure.

Epidemiology

- **Caused by a photosensitizing agent**
- **Photoprotection may not be a usual practice in patients with skin of color**
- **Often caused by antibiotics, thiazide diuretics, isotretinoin, and voriconazole**

Photosensitive drug eruptions may be less common in skin of color because of the relative photoprotection provided by the melanin especially in darker skin types. However, when photosensitive drug eruptions do occur, they present unique challenges for the practitioner educating parents and patients with skin of color. Many patients (especially those with darker skin types) may not have been accustomed during their lives to practicing photoprotection. In general studies not particularly related to drug photosensitivity, parental use of photoprotective measures was directly related to children's sun protection practices [9]. The most common photosensitizing drugs are antibiotics (especially tetracycline family), isotretinoin, thiazide diuretics, amiodarone [10], NSAIDs, antidepressants, psoralens, and voriconazole [11]. Some photosensitivity can also be seen as a side effect of topical retinoid use.

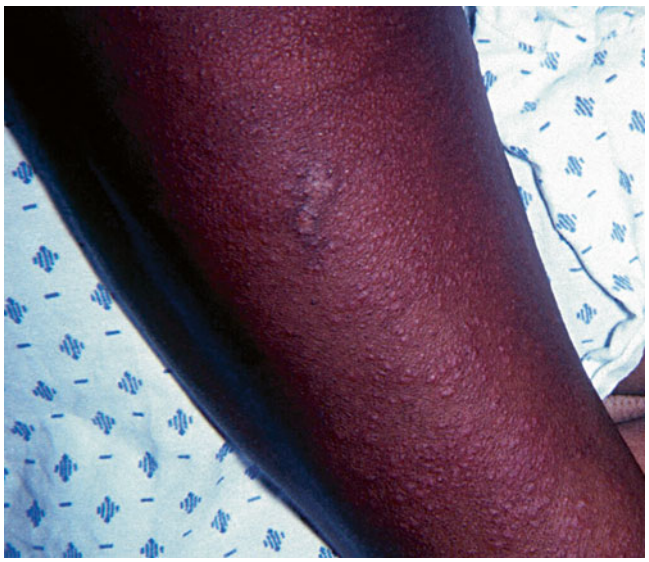

Fig. 35.3 Papules of the extensor arm in a photosensitive eruption from a thiazide diuretic

Clinical Presentation

- **Erythema**
- **Papules**
- **Photodistributed pattern**

Photosensitive drug eruptions have erythema and papules in a photodistributed pattern. In richly pigmented skin, the erythema can be more difficult to appreciate (Fig. 35.3).

Treatment

- **Withdraw offending agent**
- **Photoprotective measures**
- **Topical and oral steroids may be useful**

Withdrawal of the offending drug is the initial step for treatment. Sun avoidance and/or use of sunscreen are recommended

especially if the drug is felt to be essential and is continued. Topical or oral corticosteroids can provide additional relief.

Prognosis

Once the offending drug is withdrawn and UV exposure is avoided, the eruption typically improves.

Ongoing Research

Determination of factors which predispose individuals to photosensitive drug eruptions is essential for minimizing these reactions.

Conclusion

Avoidance of UV exposure is important for a child with a photosensitive drug eruption.

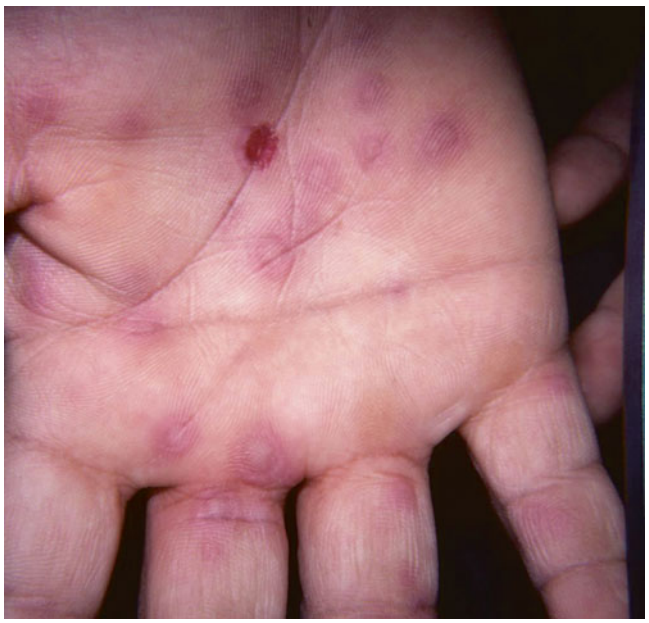

Fig. 35.4 Target lesions of erythema multiforme minor on the palms

Erythema Multiforme Minor

Introduction

Erythema multiforme minor (EM) is an immune-mediated condition which can occur in response to infectious or pharmacologic inciting agents. The minor designation denotes no mucous membrane involvement.

Epidemiology

- **Same incidence in skin of color**
- **Associated with herpes simplex virus and *Mycoplasma pneumoniae***

The most common associated infectious agent in children is herpes simplex virus, although causation from *Mycoplasma pneumonia* infection has been reported [12]. The most common pharmacologic agents associated with EM minor include nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, and antibiotics. The incidence of EM in skin of color is the same as the general population.

Clinical Presentation

- **"Dusky" center**
- **Target lesions**
- **Lesions on extensor extremities**

The "target" lesion is the most well-known lesion of EM. It consists of a "dusky" center (from epidermal necrosis) with an annular edematous surround (Fig. 35.4). EM lesions are most often located on the extensor extremities, but can occur on any area of the body. The "multiforme" designation of the term refers to changing appearances of the lesions (not to any movement of the lesions).

Treatment

- **Anti-viral medication for herpes virus-associated lesions**
- **Discontinue medication**
- **Topical corticosteroids**

If the EM is due to Herpes Simplex virus, antivirals such as acyclovir are recommended [12]. Withdrawal of any offending pharmacologic agent is indicated as an initial measure. Topical corticosteroids have been reported as useful. The use of systemic corticosteroids remains controversial [12].

Prognosis

EM minor has a good prognosis; however, in skin of color, postinflammatory dyspigmentation may occur.

Ongoing Research

Continued vigilance for associations of erythema multiforme minor with new medications as they are released is warranted.

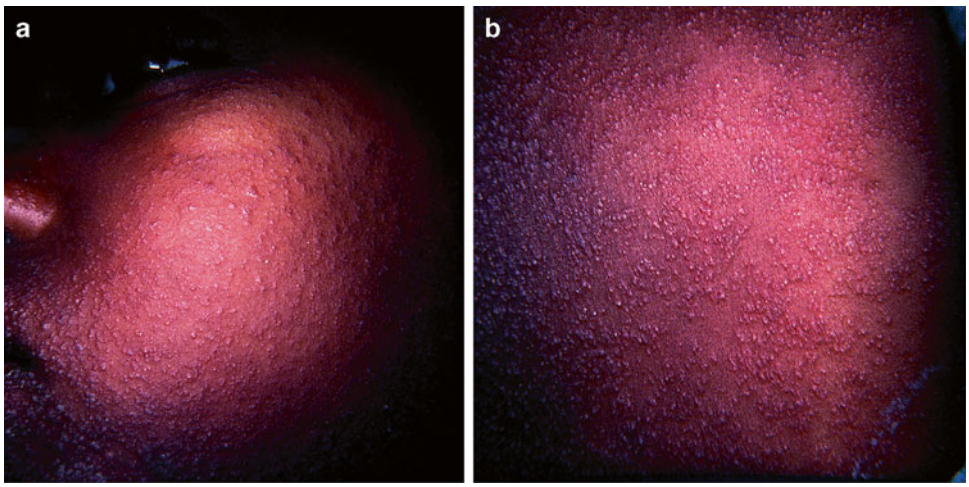

Fig. 35.5 (**a**) Diffuse papules of the cheek in a patient with DRESS syndrome. Some periorbital swelling was present. (**b**) Closer view of the papules

Conclusion

Erythema multiforme minor is a hypersensitivity reaction which can be triggered by infectious agents or drugs.

DRESS Syndrome

Introduction

DRESS syndrome, aka drug reaction with eosinophilia and systemic symptoms, is a drug reaction with characteristic features. Other terms which have been applied are: (a) Drug-induced hypersensitivity syndrome and (b) Phenytoin hypersensitivity syndrome.

Epidemiology

- **Increased in African Americans**
- **Associated with mutations in drug detoxification genes**
- **Associated with anticonvulsants, antibiotics, NSAID's among others**

Phenytoin had been the medication most often associated with DRESS; however, other medications have since been identified as causative agents. Those medications include anticonvulsants, antidepressants, antihypertensives, antimicrobials, antivirals, biologics, and nonsteroidal anti-inflammatory agents (NSAIDs) [13].

Mutations in the genes encoding drug detoxification are associated with a higher risk of DRESS. Since the mutations are inherited in an autosomal dominant fashion, familial cases are reported. There is an increased incidence in African Americans [13].

The reaction develops 2–6 weeks after the drug is started.

Clinical Presentation

- **Erythematous morbilliform eruption**
- **Facial swelling**
- **Fever**

Patients with DRESS are noted to have an erythematous morbilliform eruption. The lesions are present on the face, upper trunk, and extremities. Mucosal involvement can be noted with mouth erosions and cheilitis, but the mucosal features are not as consistently present nor are they as severe as in Stevens–Johnson syndrome. In addition, the children are febrile and ill-appearing. Facial swelling is a common feature. In children of color, the erythema may not be easily appreciated (Fig. 35.5).

Extracutaneous organ systems affected in DRESS include hepatic, renal, hematologic, pulmonary, gastrointestinal, and endocrine systems [13]. The liver is the most common visceral organ affected. Hypereosinophilia is present in approximately 30 % of patients.

Treatment

- **Discontinue offending agent**
- **Supportive care**
- **Systemic corticosteroids**

Withdrawal of the offending agent, systemic corticosteroids, and supportive care are the recommended therapies [14].

Prognosis

The mortality rate in DRESS is approximately 10 % (most often from hepatic complications). Walsh et al. [15] suggested that an erythema multiforme-like eruption in DRESS could be prognostic for more severe hepatic involvement.

Ongoing Research

Identification of the detoxification genes has been useful for some predictions for families susceptible to DRESS. Further genetic characterization could assist in decision making for drug choices prior to initiating a specific agent in the future.

Conclusion

DRESS is a hypersensitivity reaction with a 10 % mortality rate which has an increased incidence in African Americans.

Stevens–Johnson Syndrome

Introduction

Stevens–Johnson syndrome (SJS) is a hypersensitivity reaction to medications or infectious agents. Stevens–Johnson syndrome and Toxic Epidermal Necrolysis (TEN) are considered by some to be part of the same spectrum and will be discussed together in this section. The syndrome is a consequence of toxic injury to the keratinocytes and mucosal epithelial cells.

Epidemiology

- **Hypersensitivity reaction to drugs or *Mycoplasma pneumonia***
- **Some genetic predilection**

The drugs most often cited as causative agents for SJS are sulfa containing drugs, anticonvulsants, and nonsteroidal anti-inflammatory agents [16, 17]. *Mycoplasma pneumoniae* has been implicated in a small percentage of patients and may have less severe manifestations [18, 19]. Family history is pertinent since a genetic predisposition is present in some individuals.

Clinical Presentation

- **Presents with fever, malaise, and headache**
- **Patients have two or more mucosal sites with erosions**
- **Subepidermal bullae and erosions show lack of pigment**

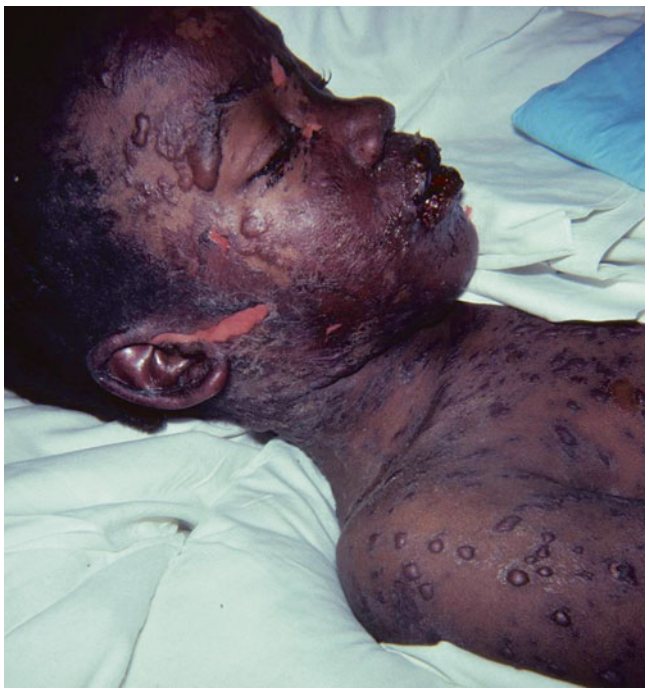

Fig. 35.6 Patient with Stevens–Johnson Syndrome. Note the lack of pigmentation in the eroded area and the erosions of the lips

The usual clinical presentation involves rapid onset of fever, malaise, and headache. The children are ill-appearing. Bullous lesions, then erosions, develop on the mucous membranes (two or more sites) and skin. Since the bullae are subepidermal, the eroded surfaces lack pigmentation (Fig. 35.6). A frozen section of a blister roof will show several layers of epidermal cells. Nikolsky's sign is positive in involved areas.

Gastrointestinal involvement may be manifested by dysphagia due to esophageal erosions, abdominal pain, diarrhea, and later malnutrition.

Treatment

- **Discontinue the offending drug**
- **Admit to a burn unit**
- **IVIG alone or in combination with systemic corticosteroids**

Prompt discontinuation of the offending agent is vital. Supportive care in a burn unit has been noted to result in improved outcomes. Ophthalmology consult is recommended if eye involvement is noted [20]. Downey et al. [21] discuss the use of IVIG rather than systemic corticosteroids. IVIG in combination with systemic corticosteroids has been efficacious [22]. Plasmapheresis has also been reported as efficacious [22].

Prognosis

Mortality for SJS and TEN is approximately 5–10 % and 30 %, respectively. A significant source of morbidity is ocular sequelae [23]. Residual dyspigmentation can be significant in skin of color.

Ongoing Research

Research regarding genetic susceptibility can help to predict which individuals may have an increased risk for developing SJS and/or TEN.

Conclusion

Prompt diagnosis of SJS and /or TEN can reduce the mortality associated with these diagnoses.

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Infantile Acropustulosis

36

Nanette B. Silverberg

Abstract

Infantile acropustulosis is an inflammatory, neutrophilic dermatosis of the palms and soles, seen primarily in children in the first 1–2 years of life. The diagnosis is usually clinical—identified by recurrent crops of vesicopustules developing over the palms and soles extending up over the dorso-ventral margin and wrist, but not onto the rest of the body. Lesions can be triggered by scabies or hand-foot-mouth disease. Identification of the former and therapy of the same may be necessary. Therapy traditionally involves usage of mid- to high-potency topical corticosteroids. Systemic dapsone has been used, but dosages are limited by hemolysis and careful G6PD screening is needed, given that deficiency is an X-linked recessive disorder in Black, Middle Eastern, and Asian children. Resolution by age 3 is generally universal.

Keywords

Infantile acropustulosis • Inflammatory • Neutrophilic dermatosis • Palms • Soles • Vesicopustules • Dorso-ventral margin

Introduction

Infantile acropustulosis is an uncommon condition that affects primarily Black children [1], usually from infancy through 1–2 years of age [2]. Disease is quite pruritic and can be precipitated by prior infections such as scabies and hand-foot-mouth disease. Therapy with topical corticosteroids is often effective.

Epidemiology

- **Infantile acropustulosis is a rare disorder of infants and toddlers.**
- **Affects African-American/ Black, Asian, and Hispanic Children, and occasionally Caucasian children.**
- **Affects international adoptees from Vietnam, China, Ethiopia, Guatemala, and Russia.**
- **Males of color are most likely affected by the disorder.**
- **Occurrence is worldwide and may be triggered by scabies and/or hand-foot-mouth disease.**

Infantile acropustulosis is an inflammatory, neutrophilic dermatosis of the palms and soles that affects infants and toddlers, especially Black children [3], although any race or ethnicity can be affected. Presence in Hispanic children has been noted in one study that linked infantile acropustulosis to prior scabies. Scabies can be a precipitant of the illness in 50 % of cases [4]. Twenty and thirty percent of cases respectively will have atopy or a relative with atopy [5] (Fig. 36.1).

Infantile acropustulosis occurs worldwide. Reports in East Asian children and occasionally Caucasian children have appeared in the literature [6]. Onset is usually in infancy or toddler years, especially between 2 and 10 months of age [6], but cases do occur even in adolescents, often being precipitated by or mistaken for scabies in this setting. Resolution by age 2 is usual [7]. Cases reported in international adoptees highlight that the lesions are often misdiagnosed as scabies, and that more than half of cases go undiagnosed. The setting

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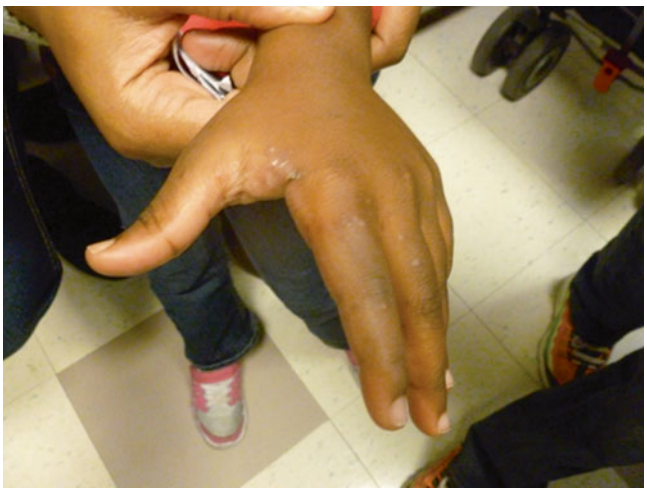

Fig. 36.1 Typical pustules and vesicles infantile acropustulosis occurring on the hands in an 18-month-old boy and month after clearance of scabies

of crowded unclean prior living conditions can be a risk factor [8]. An association with underlying atopic dermatitis was also noted in a series of international adoptees [8].

Clinical Features/Diagnosis

- **Diagnosis is clinically made by the presence of pruritic vesicopustules over the palms and soles extending up to the wrist and calf in some cases.**
- **Exclusion of scabies as a diagnosis is needed and can be accomplished by mineral oil preparation.**

Infantile acropustulosis is a recurrent, pruritic, vesicopustular disorder of the palms and soles [4]. 1–2 mm papules and pustules of the soles (100 %) and hands (94 %) will be noted in infantile acropustulosis [8]. The disease is usually seen in young patients within the first 1–2 years of life. Biopsy demonstrates necrolysis of keratinocytes followed by formation of intraepidermal pustules with neutrophils and eosinophils [9]. Peripheral eosinophilia and high IgE levels have been demonstrated in some cases [10, 11]. A mineral oil preparation can be performed to rule out scabies. Direct immunofluorescence is negative for these lesions.

Differential diagnosis includes pustular psoriasis [12], allergic contact dermatitis, and scabies, which must always be ruled out. Recently, cases of hand-foot-mouth disease have been reported with severe lesions of the extremities mimicking acropustulosis [8]. Similarly, IL-1 receptor antagonist deficiency has been described to cause infantile acropustulosis mimicking infantile pustular psoriasis of the extremities [13].

Treatment

- **Brief application of Class I or II topical corticosteroids usually clears specific episodes.**
- **Disease remission can be achieved through the usage of oral dapsone in patients who do not have G6PD deficiency.**

Therapy of infantile acropustulosis was originally systemic dapsone therapy which was complicated by risk of hemolysis and methemoglobinemia, requiring pretreatment G6PD screening (especially in children of color) and ongoing blood counts [14]. More recently, this therapy has been replaced with usage of mid- to high-potency topical corticosteroids which are highly effective, although relapses and recurrences can be noted [15]. In the setting of suspected scabies, therapy of scabies should first be initiated. A case report highlighted good response in a 9-month Japanese male infant with topical maxacalcitol 0.0025 % (Oxarol, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) applied twice a day for one week followed by usage every 3–4 days with complete crop cessation and clearance of lesions [16].

Research

This author is currently in the process of publishing her experience with the usage of topical dapsone 5 % gel twice daily for corticosteroid-resistant lesions. Monitoring of blood counts to identify hemolysis should be done in these cases until such time as it is understood how much dapsone is absorbed by infants and children through the palms and soles.

Conclusions

Infantile acropustulosis is a chronic but temporary vesicopustular disorder of infancy which resolves with time. Appearance may be more common in Black male infants, but reports have been made worldwide. Usage of topical medications has supplanted oral dapsone for the therapy of the disease.

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Pediatric Mastocytosis

37

Nisha Suyien Chandran

Abstract

Mastocytosis refers to a heterogeneous group of disorders characterized by the abnormal infiltration of mast cells into tissues including skin, bone marrow, liver, spleen, and lymph nodes. Mastocytosis in both adults and children is a clonal mast cell disease due to activating mutations in the KIT gene. Pediatric mastocytosis is typically limited to the skin and has a benign prognosis. Nevertheless, cutaneous mastocytosis in children can be associated with systemic symptoms due to mast cell degranulation and release of mast cell mediators, even when there is no systemic infiltration. Treatment of pediatric mastocytosis is aimed at preventing and controlling skin and systemic mast cell activation symptoms. Therapy is divided into topical and systemic forms, as well as antimediator and cytoreductive therapies; these should be tailored according to the grade of symptom severity in the individual patient.

Keywords

Mast cells • c-KIT • Childhood • Mastocytoma • Urticaria pigmentosa • Diffuse cutaneous mastocytosis • Tryptase

Background/Introduction

Key points

- *Childhood mastocytosis is a clonal mast cell disease due to activating mutations in the KIT gene.*
- *Childhood mastocytosis is typically limited to the skin.*
- *Cutaneous and systemic mastocytosis are defined according to the WHO classification.*
- *Familial forms of cutaneous mastocytosis are linked to germline and somatic mutations in the KIT gene.*

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Mastocytosis refers to a heterogeneous group of clinical syndromes characterized by the abnormal infiltration of mast cells into various tissues including the skin, bone marrow, liver, spleen, and lymph nodes with or without the concomitant release of chemical mediators by these cells [1].

The heterogeneity of mastocytosis is exemplified by its presentation as two primary age-related patterns: pediatric-onset mastocytosis and adult-onset mastocytosis, which may differ in their clinical manifestations and disease outcomes. The typical presentation of pediatric-onset mastocytosis is that of cutaneous mastocytosis (CM) which consists of cutaneous manifestations, namely, mastocytoma, urticaria pigmentosa, and less commonly, diffuse cutaneous mastocytosis. The clinical course is variable but majority of children with CM experience resolution of skin lesions by adolescence [2]. Systemic mastocytosis is rare finding in children. Only two cases of systemic involvement were described in one of the largest pediatric series involving 173 Australian children with cutaneous mastocytosis [3]. In contrast, adult-onset mastocytosis often manifests with systemic involvement

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Table 37.1 Classification of mastocytosis according to WHO recommendations

Cutaneous mastocytosis
(a) Solitary mastocytoma
(b) Maculopapular cutaneous mastocytosis/urticaria pigmentosa
(c) Telangiectasia macularis eruptiva perstans
(d) Diffuse cutaneous mastocytosis
Indolent systemic mastocytosis (ISM)
Systemic mastocytosis with associated clonal hematologic disease (SM-AHNMD)
Aggressive systemic mastocytosis (ASM)
Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)
Extracutaneous mastocytoma

(systemic mastocytosis) and exists for the lifetime of the patient with increase in extent and severity over time. Skin lesions in adults usually indicate the presence of systemic disease [4, 5].

The WHO classification defines seven forms of mastocytosis (Table 37.1) [6]. An eighth form, though not yet included in the WHO classification, is the recently characterized well-differentiated systemic mastocytosis (WDSM) [7, 8].

Mast cells originate from hematopoietic progenitor cells in the bone marrow and migrate in a precursor state to connective tissue where they acquire their mature phenotype [9]. Mast cell precursors mature via activation of the transmembrane receptor CD117 with intrinsic tyrosine kinase activity, also known as KIT. Human c-KIT is a proto-oncogene that encodes for KIT. Coupling of KIT with the soluble KIT ligand, also known as stem cell factor (SCF), induces mast cells to express the high-affinity IgE receptors ($F_{CE}RI$) and proliferate [10]. The KIT receptor contains five domains: the extracellular domain, the transmembrane domain, the juxtamembrane domain, and two tyrosine kinase domains (tyrosine kinase 1 and tyrosine kinase 2, also known as the activation loop) [10].

Mutations in c-KIT activate tyrosine kinase activity independent of SCF binding. These are termed "self-activating mutations" and are in turn capable of inducing hyperproliferation of KIT-expressing cells [10]. Two types of c-KIT mutations have been described: regulatory type, which are located within the extracellular and juxtamembrane intracellular part of KIT, and enzymatic site type, which are located in the tyrosine kinase domain. Therapeutic implications are implied as the former is sensitive to the tyrosine kinase inhibitor imatinib mesylate while the latter is insensitive (see "Treatment" below) [11].

Adult mastocytosis has clearly been shown to be related to mutations in c-KIT resulting in clonal proliferation of mast cells [12, 13]. Majority of adult patients with SM have mutations in D816V (exon 17) on the activation loop domain [14]. In contrast, pediatric mastocytosis was formerly regarded as a reactive disease due to hyperplasia of mast cells to abnormal stimuli [15]. However, recent evidence reveals that pediatric mastocytosis is in fact, similar to adults: a clonal disease due to self-activating mutations in the c-KIT gene [7]. Analysis of the entire c-KIT sequence from cutaneous biopsies of 50 children with mastocytosis by Bodemer et al. demonstrated somatic mutations in exon 17 in 42 % of cases, with 36 % harboring mutations in D816V; mutations outside exon 17 were observed in 44 %, namely in exons 8, 9, and 11; all mutations constitutively activated c-KIT [16]. A study of 12 Japanese children similarly found D816V mutations in 10 of the patients [17] while a series of 9 cases of solitary mastocytomas identified c-KIT mutations in six cases (67 %), including 3 with the D816V mutation and 3 with an internal tandem duplication (p.A502_Y503dup) in exon 9 [18].

Familial forms of diffuse cutaneous mastocytosis have been reported. Germline mutations in c-KIT including mutations in the transmembrane domain of KIT A533D in members of 3 generations of a Scottish family and mutations in the extracellular domain of KIT S451C in 2 generations of a Han Chinese family have been described [19, 20]. Members of an Austrian family were found to have somatic mutations in c-KIT S849I and M835K (both exon 18) which was associated with a condition suspicious of mast cell activation syndrome and a tendency to incomplete resolution in adulthood [21]. Autosomal dominant inheritance of familial diffuse cutaneous mastocytosis has been suggested in a Japanese mother and her 3 daughters though no genetic studies were performed [22].

In essence, mastocytosis in children, like in adults, is a clonal disease due to self-activating mutations in the c-KIT gene.

Epidemiology

Key points

- *Most lesions of cutaneous mastocytosis in childhood appear in the first 2 years of life.*
- *Pediatric mastocytosis is more common in the Caucasian population compared to Asians or Africans.*
- *Pediatric mastocytosis is more common in males with skin of color.*

Age

Most of the lesions of pediatric mastocytosis (55–97 %) appear during the first 2 years of life [2, 23–26]. Indeed, series from Mexico and Poland found that 92 and 94 % of cutaneous lesions occurred during the first year of life

[23, 26]. The occurrence of different subtypes of cutaneous mastocytosis at different ages has been described. 40 % of mastocytomas occurred at birth and almost all by the age of 1 year in a series of Israeli children [2]. In contrast, only 20 % of the patients with urticaria pigmentosa had lesions present at birth while 80 % did so by the age of 9 months. Conversely, Kiszewski et al. found no correlation between the type of mastocytosis and the age of onset in a Mexican cohort.

Sex

European and American series report no gender predilection [27, 28], while a higher male:female ratio exists in series from Israel and Mexico (1.5:1 in Ben-Amitai and 1.8:1 in Kiszewski, respectively) [2, 23].

Race

A genetic factor could explain these differences amongst various ethnic groups. Pediatric mastocytosis seems to be more common in Caucasians [27]. Reports of Asian or African children exist only as scattered case reports in the literature.

Clinical Presentation

Key points

- *Pediatric cutaneous mastocytosis is typically divided into mastocytoma, urticaria pigmentosa, and diffuse cutaneous mastocytosis.*
- *Cutaneous mastocytosis in children can be associated with systemic symptoms due to mast cell degranulation and release of mast cell mediators, even when there is no systemic infiltration. Many stimuli can trigger mast cell degranulation.*
- *Elevated serum total tryptase levels indicate extensive skin involvement and higher risk for severe mast cell activation symptoms. Extent of skin involvement also parallels symptom severity.*

The typical presentation of pediatric mastocytosis consists of cutaneous lesions. In comparison to adults, bone marrow biopsies are not routinely performed or indicated and when they are, technical difficulties make it difficult to obtain significant results. Consequently, a definitive status of cutaneous or systemic involvement in children is usually not feasible (Table 37.2). Therefore, a working classification of pediatric mastocytosis based on the WHO criteria and the morphological appearance of lesions is adopted [7]:

Table 37.2 Diagnostic criteria for systemic mastocytosis according to WHO recommendations [6]

Major
Multifocal dense infiltrates of mast cells (MC) (MC aggregates of 15 or more cells) in bone marrow and/or other extracutaneous organs, confirmed by special stains
Minor
(a) In MC infiltrates in bone marrow or other extracutaneous organs, 25 % or more of MC are spindle shaped; or in bone marrow, 25 % or more of MC are atypical
(b) *c-kit* point mutation at codon 816 in bone marrow or blood or other extracutaneous organs
(c) Immunophenotyping of MCs in bone marrow, blood, or other extracutaneous organs that co-express CD2 or/and CD25
(d) Serum total tryptase levels persistently over 20 ng/ml (not valid if patient has associated clonal hematological non-MC disease; AHNMD)[a]
If one major and one minor or three minor criteria are fulfilled, then the diagnosis is systemic mastocytosis

[a]In acute myeloid leukemia, myelodysplastic syndrome, or myeloproliferative syndrome, elevated serum tryptase levels have been detected without increase in mast cell numbers or signs of mastocytosis

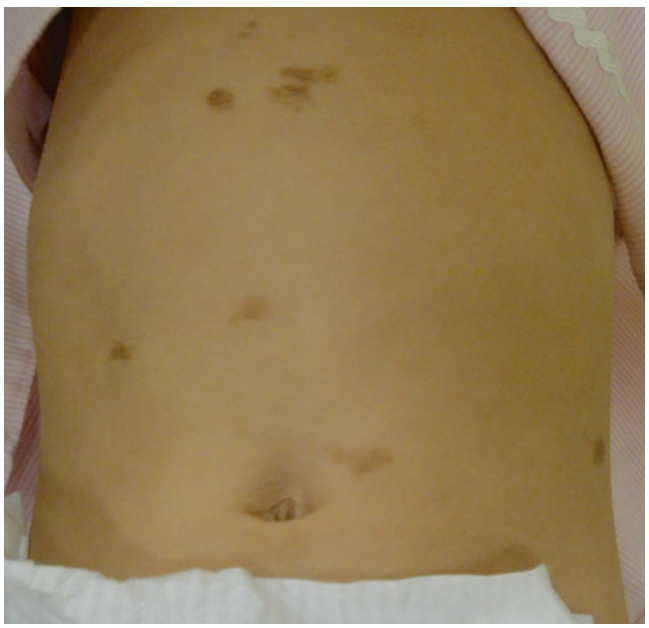

Fig. 37.1 Urticaria pigmentosa: *red-brown* macules and plaques (courtesy of Dr Mark Koh, MD)

1. Mastocytoma
2. Urticaria pigmentosa
3. Diffuse cutaneous mastocytosis

Urticaria pigmentosa (UP) is the most common form of CM in children and represents 70–90 % of all cases [29]. It is sometimes referred to as maculopapular CM. The lesions range from red to brown to yellow in color, are occasionally telangiectatic, and present as multiple macules, papules, plaques, or small nodules (Fig. 37.1). Stroking a lesion leads to wheal and flare formation. This response is known as

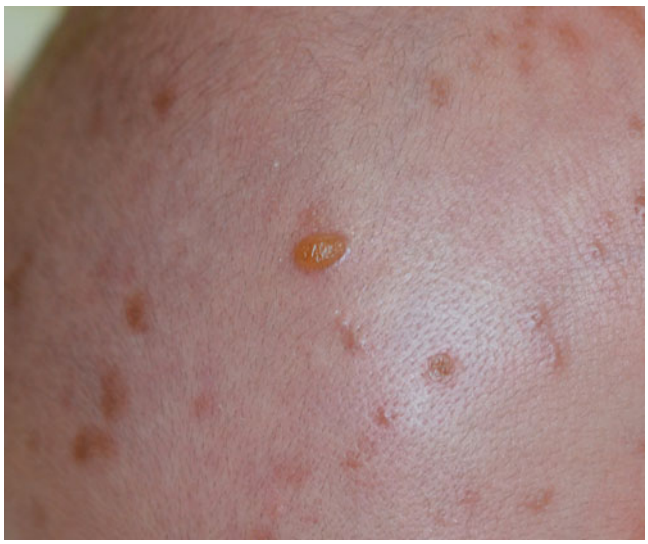

Fig. 37.2 Blister formation in urticaria pigmentosa (courtesy of Dr Mark Koh, MD)

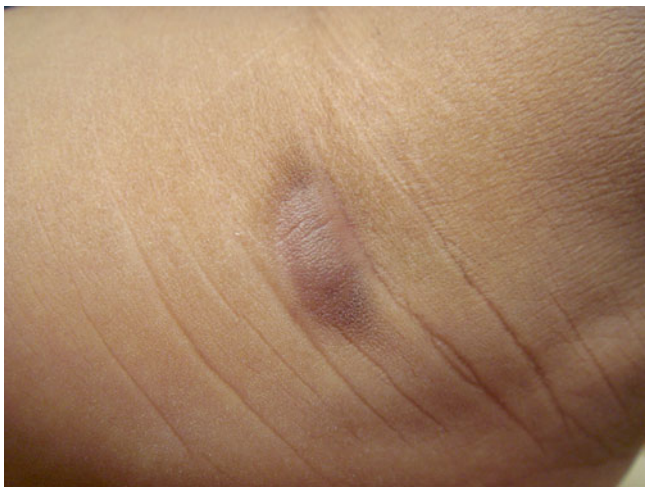

Fig. 37.3 Mastocytoma: solitary *red-brown oval* nodule (courtesy of Dr Mark Koh, MD)

Darier's sign and is considered clinically diagnostic [30]. Blister formation can also occur (Fig. 37.2).

Mastocytoma is defined as a solitary round-to-oval elevated lesion, usually present at birth (Fig. 37.3). It represents 10–30 % of cases of pediatric mastocytosis. Such lesions can vesiculate and blister especially with application of mast cell degranulators such as polymyxin B. Most lesions resolve by puberty, but persistent lesions have been described in adults [31].

Diffuse cutaneous mastocytosis (DCM) is the rarest form of CM, accounting for 1–3 % of cases. It generally presents in the neonatal period. Large areas of skin are infiltrated by mast cells. Two variants of DCM have been described. The first type describes extensive blistering and erythroderma early in life which can mimic staphylococcal scalded skin syndrome [32, 33]. Patients with the second type have extensive yellow-orange smooth-to-leathery skin with minimal blistering [34–36].

Table 37.3 Proposed modified classification of cutaneous mastocytosis

Classification of cutaneous mastocytosis
1. Maculopapular cutaneous mastocytosis
2. Plaque-type cutaneous mastocytosis
3. Nodular cutaneous mastocytosis/mastocytoma (i.e., solitary or multiple)
4. Diffuse cutaneous mastocytosis
5. Telangiectatic cutaneous mastocytosis

Adapted from Hartmann and Henz [37]

In reality, the WHO classification may be an oversimplification of the various forms of CM. Descriptions of patients in the literature show overlapping features that do not fit neatly into a particular subtype, based on traditional classification. For example, Hartmann et al. have argued that UP or maculopapular CM has varied clinical appearances and disease courses. Maculopapular CM with small lesions that occurs in children and in adults rarely resolves spontaneously and is often eventually categorized as ISM. In contrast, plaque-type CM, which is often grouped under maculopapular CM, as well as nodular CM or mastocytomas (single or multiple), has a tendency to resolution [37]. The authors have proposed a modified classification of cutaneous mastocytosis (Table 37.3). Torrelo et al. have argued that the term DCM is very ambiguous: very extensive forms of UP with ISM and extensive large mastocytoma-like nodular lesions with WDSM have also been included [7]. The same authors have also argued that different clinical manifestations classified as UP are known to fade away, develop into ISM, or evolve into WDSM. A case series by Azana et al. reported spontaneous resolution in all 67 cases of pediatric UP in a Spanish population, while Ben-Amitai et al. reported complete resolution in only 56.4 % of 180 Israeli children with UP, again highlighting different variations within the same subset [2, 38].

Mastocytosis can involve unusual anatomical locations and associations. Vulval mastocytosis was reported in two Spanish females aged 5 and 8 years [39]. Intertriginous CM involving the axillae and groins occurred in a 16-year-old Chinese male patient [40]. DCM was associated with a large bathing trunk nevus in a 4-year-old Indian male while maculopapular CM was associated with the epidermal nevus syndrome in a 2-year-old Japanese male [41, 42]. Congenital scarring alopecia was reported in a 3-year-old Korean female with UP and a mastocytoma [43].

Dermoscopy has recently been promoted as a feasible method for diagnosis and subclassification of cutaneous mastocytosis. Vano-Galvan et al. described four dermoscopic patterns in a large Spanish cohort of 127 patients (61 children

and 66 adults): yellow-orange blot, pigment network, reticular vascular pattern, and (most frequently) light-brown blot. The light-brown blot pattern accounted for most of the maculopapular CM and plaque-type mastocytosis, while the reticular vascular pattern was found in all patients with telangiectasia macularis eruptive perstans and a small proportion with maculopapular CM. The yellow-orange blot pattern was described in all children with mastocytoma and half of all patients with nodular mastocytosis . These dermoscopic patterns also showed histological correlation. Interestingly, the need for daily antimediator therapy was higher among patients with a reticular vascular pattern compared to other dermoscopic patterns [44].

Symptoms

CM in children can be associated with systemic symptoms due to mast cell degranulation and release of mast cell mediators, even when there is no systemic infiltration. These cutaneous symptoms include flushing, dermographism, and pruritus, which may occur spontaneously or in response to specific stimuli. Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea; hyperacidity and peptic ulcer disease are rare in children. Other symptoms include dyspnea, headache, fatigue, lethargy, or neuropsychiatric symptoms. Children with extensive forms of cutaneous mastocytosis are at risk of pseudoanaphylactic reactions [7].

A variety of stimuli and agents are known to activate/trigger mast cells (Table 37.4). In children, the main trigger is a change in temperature, followed by irritability, fever, and teething [46].

Various noninvasive methods have been studied to estimate the risk of severe systemic symptoms, including anaphylaxis, and the risk of disease progression in children with CM.

Table 37.4 Clinically relevant mast cell degranulators [29, 46]

Physical stimuli
Heat
Cold
Sudden changes of temperature
Mechanical friction or pressure
Sunlight
Emotional factors
Stress
Anxiety
Sleep deprivation
Infectious diseases with fever
Viral (upper respiratory tract infection)
Bacterial (bronchitis, pneumonia)
Drugs
NSAIDs
Alcohol
Narcotics (morphine, codeine, and derivatives)
Cough medication (dextromethorphan, dimemorfan)
Acetylsalicylic acid
Procaine
Polymyxin B
Amphotericin B
Vancomycin
Atropine
Thiamine
D-tubocurarine
Quinine
Radiographic contrast media containing iodine
Scopolamine
Gallamine
Decamethonium
Reserpine
Foods
Aged cheese
Alcohol
Chocolate
Strawberries
Miscellaneous
Dentition, e.g., teething and dental procedures
Vaccinations
Surgery
Endoscopic procedures

Tryptase Parallels Extensive Skin Involvement and Symptom Severity

The most reliable marker for severity of mastocytosis is serum tryptase [4, 47, 48]. In adults, total serum tryptase levels correlate with the type and severity of mastocytosis. Levels below 20 ng/ml usually indicate cutaneous mastocytosis without systemic involvement while levels above 20 ng/ml are associated with ISM; even higher levels indicate ASM. Serum tryptase levels permanently over 20 ng/ml are a minor criterion for systemic mastocytosis. However, up to 25 % of adults with proven systemic mastocytosis have serum tryptase levels below 20 ng/ml [49].

In children, the relationship between elevated serum tryptase levels and systemic mastocytosis has not been established. Levels are, however, useful to predict symptom severity. Serum tryptase levels correlated with a mastocytosis severity scoring system (SCORMA) in a group of 64 Dutch patients (31 children and 33 adults) [47]. A large Spanish study of 111 children with CM showed a strong correlation between serum baseline total tryptase levels and extent of skin involvement as well as symptom severity [7]. Unlike adults, a serum tryptase higher than 20 ng/ml in children does not translate to a diagnosis of systemic mastocytosis, which requires bone marrow studies that are not routinely performed. Rather, an elevated serum baseline total tryptase level reflects

children with extensive skin disease and higher risk of severe, even life-threatening mast cell activation symptoms. Brockow et al. further highlighted that extensive blistering in children with mastocytosis, instead of extensive flushing or pruritus, should be regarded as a predictor for severe complications in children with mastocytosis [48].

It is worth noting that despite evidence for correlation between serum tryptase and cutaneous extent of mastocytosis, there are a small number of children with minor forms of CM who have persistently elevated levels; the significance of elevated serum tryptase in the outcomes of these children is unknown [7]. Other mediators such as histamine and *N*-methyl histamine have been correlated with increased mast cell numbers in the skin, but levels vary with the age of the child [50].

Skin Severity Parallels Symptom Severity

Serum tryptase is not the only marker that can predict symptom severity. The severity of skin disease itself has been shown to parallel symptom severity. In a cohort of 67 American children (61 % Caucasian, 10 % African-American, 10 % Asian, and 3 % Hispanic) with maculopapular CM, the maximum number of skin lesions and the number of skin symptoms were significant predictors for the number of systemic symptoms [51]. In contrast, an earlier study by Brockow et al. [10] revealed a correlation between the extent of cutaneous involvement with symptom extent and severity in adults with maculopapular CM but not in the pediatric cohort [52]. Due to the extent of skin symptoms in DCM, severe systemic symptoms including whole body flushing, gastrointestinal bleeding, hypotension, hypovolemic shock, and even death have been reported in a 17-month-old Irish male [53].

Treatment

Key points

- *Treatment of pediatric mastocytosis is aimed at preventing and controlling skin and systemic mast cell activation symptoms*
- *Therapy can be divided into topical and systemic forms, as well as antimediator and cytoreductive therapies; these should be tailored according to the grade of symptom severity in the individual patient*
- *Anesthesia is generally safe in the pediatric mastocytosis population; however meticulous planning should be ensured to manage potential cardiovascular decompensation*

General Concepts

The treatment of pediatric mastocytosis is not curative but instead aimed at preventing or controlling skin and systemic mast cell degranulation symptoms with the anticipation that skin lesions will fade as the child grows.

A four-grade scale for mastocytosis severity from mast cell degranulation, which is also applicable to children, has been established by consensus guidelines [4, 45]. This grading severity can be used to determine suitable treatments.

1. Grade 0: no symptoms
2. Grade 1: mild symptoms, no therapy required
3. Grade 2: moderate symptoms, kept under control with antimediator-type drugs
4. Grade 3: severe symptoms, not sufficiently controlled with therapy
5. Grade 4: severe adverse events that require emergency therapy and hospitalization

Avoidance of Triggering Factors

A variety of stimuli and agents are known to activate mast cells (Table 37.4). Measures should be undertaken by parents and patients to recognize and avoid or control these. For example, an ideal ambient temperature can be adjusted based on the child's response. Castells et al. recommend a trial of lukewarm water for bathing (20–23 °C) and air-conditioning at 26 °C [29].

Topical Therapy

Cutaneous lesions with pruritus and flare can be treated with water-soluble sodium cromoglycate cream and lotion [54]. Topical corticosteroids can prevent blistering, while topical zinc sulfate and antibacterials are useful for denuded skin [55]. Topical therapy can be used for all cutaneous lesions of all grades of mastocytosis severity.

Systemic Therapy

The cornerstone of treatment of all categories of mastocytosis is symptom control. Antimediator therapy takes the form of drugs used for symptom control or receptor signaling for these mediators, and on occasion by reducing the production of mast cell mediators or preventing the release of mediators from mast cells [56].

Both sedating and non-sedating H1 antihistamines have been shown to be useful in decreasing pruritus, flushing, urticaria, tachycardia, and symptom severity of anaphylaxis [57, 58]. In particular, diphenhydramine, hydroxyzine, and cetirizine have proven to be useful in children.

Most experts do not regard the H1 antihistamine ketotifen as a medication unique in its class, despite its ostensible mast cell stabilizing properties [58, 59]. H2 antihistamines such as ranitidine and famotidine can be used to treat gastrointestinal symptoms associated with mastocytosis [7, 60]. H2 antihistamines can be combined with H1 antihistamines to control severe pruritus and flare [61, 62].

Oral cromolyn sodium can alleviate a variety of symptoms associated with mast cell degranulation in patients with systemic mastocytosis: gastrointestinal (diarrhea, abdominal pain, nausea, and vomiting), cutaneous (pruritus, whealing, and flushing), and central nervous (cognition) [63, 64]. In particular, studies of pediatric patients with cutaneous mastocytosis (urticaria pigmentosa and bullous mastocytosis) have reported efficacy of oral cromolyn sodium [65, 66]. Introduction with small incremental doses instead of the full dose reduces adverse effects of abdominal cramping and diarrhea [56].

Oral corticosteroids have been used for various indications in mastocytosis, albeit supported by only anecdotal evidence or case reports. In children, they are indicated for anaphylaxis or abdominal pain (with or without diarrhea) that is unresponsive to oral cromolyn sodium [29].

Leukotriene antagonists may be employed when symptoms are refractory to standard therapy. A 2-month-old male infant with systemic mastocytosis (skin and bone marrow biopsy done), prominent bullous skin lesions, and wheezing showed improvement of symptoms when monteleukast was added on to high-dose oral prednisolone, cromolyn sodium and, H1 and H2 antihistamines [67]. An 8-year-old female diagnosed with ISM (based on skin lesions of urticaria pigmentosa, symptoms of flushing, diarrhea, abdominal pain and urinary incontinence, and elevated tryptase level of 199 μg/l (normal <20 μg/l)), similarly demonstrated good response with addition of monteleukast as adjuvant therapy [68].

Oral psoralen with UVA (PUVA) has been reported to be effective in patients with bullous diffuse cutaneous mastocytosis [69, 70], and modestly useful in urticaria pigmentosa [71, 72]. Bath PUVA is not as effective. Adverse effects of PUVA include photofibrosis, non-melanoma skin cancers, malignant melanoma, and direct ocular damage [73, 74].

The value of anti-IgE therapy has been suggested in the treatment of mastocytosis, in particular patients with systemic mastocytosis who suffer from recurrent anaphylaxis [75, 76]. Omalizumab is useful in the control of mastocytosis-related symptoms. A 7-year-old Spanish female with CM (systemic mastocytosis not ruled out as parents refused consent to a bone marrow biopsy) who had atypical age-related worsening of mast cell mediator symptoms (unprovoked urticaria and anaphylaxis) despite therapy was recently reported to show significant and sustained resolution of symptoms with short-term courses of omalizumab [77]. While omalizumab is generally well tolerated, adverse effects such as an initial transient increase in mast cell mediator symptoms and intestinal and cutaneous fungal infections have been reported [78].

Cytoreductive therapy may be required for patients with systemic mastocytosis with infiltration of mast cells in multiple organs with resultant high mast cell burden and severe systemic symptoms.

Imatinib mesylate is the only FDA-approved tyrosine kinase inhibitor for use in patients with ASM without D816V KIT or with KIT mutation status unknown. Clinical trials have shown lack of efficacy in patients with exon 17 D816V KIT mutation, which accounts for the majority of patients in adults with systemic mastocytosis [79–81]. However, imatinib may potentially play a greater therapeutic role in the pediatric mastocytosis population as up to 58 % have mutations in KIT other than D816V, or lack mutations in KIT [16]. A 19-year-old Indian female with recalcitrant skin lesions diagnosed with ISM (skin and bone marrow confirmatory) and unmutated D816V KIT achieved clinical remission on treatment with imatinib mesylate [82]. Two Belgian and French Caucasian infants with DCM and exon 8 (p.Asp419del) KIT mutation similarly showed good response to imatinib mesylate [83].

In summary, topical therapies can be used for all grades of severity with cutaneous symptoms. Grade 1 and 2 diseases are treated with H1 antihistamines for cutaneous symptoms and H2 antihistamines with or without oral cromolyn sodium for gastrointestinal symptoms. Grade 3 disease is treated with daily oral cromolyn sodium and both H1 and H2 antihistamines. Oral corticosteroids, oral PUVA, or leukotriene antagonists may be added on. A trial of omalizumab or imatinib mesylate is warranted in these patients. Patients with grade 4 disease require a combination of the medications above, in addition to epinephrine and sedation for hemodynamic stabilization. Alvarez-Twose et al. recommend that early intensive antimediator therapy be given to children identified to be at risk of severe mastocytosis-related anaphylaxis on the basis of extent of cutaneous involvement and a serum baseline total tryptase level >16 μg/l [45].

Anesthetic Considerations in Mastocytosis

Children with mastocytosis need careful consideration when involved in anesthetic procedures [84].

Patients with mastocytosis may occasionally require diagnostic or therapeutic procedures which require sedation or anesthesia. Several drugs used in perioperative anesthesia (NSAIDs, opioids, muscle relaxants, sedative hypnotics, and volatile anesthetics) are reported to cause mast cell

degranulation with release of histamine and other mediators (see Table 37.4). With mast cells implicated in the pathophysiology of anaphylaxis and the increased mast cell burden in patients with mastocytosis, there is potential for profound adverse effects due to drug-induced mast cell degranulation leading to anaphylaxis in these patients. The overall reported incidence of anaphylaxis during anesthesia is estimated at 1 case per 5,000–20,000 patients per year with an increasing trend secondary to improved accounting measures [85, 86]. Indeed, the overall incidence of anaphylaxis in the patients with mastocytosis is significantly higher than in the general population [87–89].

Mast cell degranulation in patients with mastocytosis is unpredictable and does not occur consistently in any given patient [90, 91]. At present, there is no known investigation that can consistently predict mast cell degranulation in these patients [84, 90]. In addition, drug-induced histamine release from mast cells has largely been documented in in vitro or animal studies and may not reflect the human response [29].

In the adult mastocytosis population, spontaneous cardiovascular collapse as well as collapse under conditions of stress such as anesthesia and surgery has been reported [92–95]. In contrast there have been only two reported cases of nonfatal cardiovascular collapse in children with mastocytosis undergoing anesthesia and surgery. The first case concerned a white infant with bullous mastocytosis who became severely hypotensive upon repeat exposure to sufentanil [96]. The second case involved a white teenage female who developed an anaphylactoid reaction during general anesthesia after administration of midazolam, fentanyl, lidocaine, propofol, and cefazolin [97]. The diagnosis of systemic mastocytosis in this patient, based on elevated serum tryptase levels, was subsequently questioned as the WHO criteria were not fulfilled. In a retrospective series of 22 children with mastocytosis who underwent 29 procedures under anesthesia, the perioperative courses were uncomplicated without serious adverse events; prophylactic corticosteroids and antihistamines were not administered and preoperative drug skin testing was not performed [90]. A case series of six children similarly showed no severe anesthesia-related complications [91]. While it can appear that anesthetic procedures in pediatric mastocytosis patients are less treacherous than in adult patients with mastocytosis, meticulous pre-procedure preparation should nevertheless take place in view of the increased risk of anaphylaxis. Indeed, most experts advocate that cardiovascular decompensation should be a foreseeable concern in all cases of mastocytosis patients undergoing surgery [84]. Castells et al. recommend that the diagnosis of pediatric mastocytosis should not preclude the use of routine anesthetics in these patients, provided they do not have a history of adverse events. They advocate the administration of incremental doses of required drugs known to activate mast cells, such as opioids and muscle relaxants, and thorough preparation to manage possible though rare adverse events during anesthesia [29]. Notable exceptions include sufentanil and ketorolac, which have caused cardiac arrest in an infant with bullous mastocytosis and a lethal idiosyncratic reaction in an adult with mastocytosis, respectively; these anesthetic agents should be avoided in the mastocytosis population [29, 96].

A good understanding of the pathophysiology of mastocytosis is essential in planning good perioperative care. As detailed above, physical triggers of mast cell degranulation should be avoided in the perioperative setting. Thus special attention should be given to positioning and protection of pressure points in patients with mastocytosis, as should regulation of ambient temperature to reduce wide variations and reduction of emotional stress in patients.

Patients with mastocytosis may have symptoms of gastroesophageal reflux disease. Rapid sequence induction may be performed to expedite intubation of the trachea in these patients who have an increased risk of aspirating stomach contents into the lungs.

Serum tryptase is constitutively expressed in patients with mastocytosis and is a reflection of the extent of mast cell burden. Within 60 min of onset of anaphylaxis, serum tryptase is elevated over baseline; elevation may last for 2–4 h. It is prudent to perform a pre-procedure baseline serum tryptase level as an increase in tryptase level during an adverse event would be helpful to indicate mast cell activation.

As mast cells contain heparin, children with mastocytosis may demonstrate prolonged prothrombin time (PT) and partial thromboplastin time (PTT). Consequently, evaluation of coagulation profile may be considered prior to invasive procedures where blood loss is expected [29].

Routine pre-procedure skin testing and antigen-specific IgE assays for perioperative medications such as anesthetics, muscle relaxants, or opioids are not recommended. Such testing has not demonstrated a positive predictive value for adverse reactions to drugs and may unnecessarily escalate care [90, 98].

Prognosis

The evolution of children with mastocytosis may take four possible paths: fading, progression into adult ISM, progression into adult WDSM, and very occasionally progression into an early-onset ASM [7]. The exact number of children which will evolve along these paths is unknown.

Large solitary lesions (nodular classic mastocytoma and macular) likely fade away during childhood [2, 38]. Multiple nodules likely resolve or occasionally persist into adulthood in the form of a WDSM [7, 45]. Classic macular forms or papular forms most likely fade by age 18 years or occasionally evolve into adult ISM [2, 38, 45].

In the series of eight children with DCM by Heide et al., cutaneous signs disappeared in all cases before the age of 2 years. Serum levels of mast cell mediators decreased significantly in six out of eight of the children; in two of the children with limited decline in mast cell mediators, one was eventually diagnosed with ISM while a bone marrow biopsy was planned in the other [34].

In general, however, the evolution of pediatric mastocytosis is unpredictable. There is no laboratory test that predicts resolution or progression into systemic disease. c-KIT mutations have been described in both groups of patients and therefore do not aid in distinguishing them [16]. The actual frequency of systemic involvement in children with CM cannot be accurately established. A diagnosis of CM may turn out to be systemic mastocytosis when an eventual bone marrow biopsy is performed, when indicated, at an older age. Whether patients with more extensive cutaneous disease who suffer from more severe symptoms actually in fact do have systemic disease remains to be systematically evaluated. Similarly, whether patients with extensive cutaneous disease in association with systemic involvement are likely to suffer from more severe symptoms than those with extensive disease restricted to the skin, while expected, remains unknown [45]. Observation of 111 Spanish children with elevated serum total tryptase at baseline showed a progressive decline of levels with the growth of the child in parallel with clinical improvement. Potential explanations include: (1) Decrease in the total mast cell burden to body mass ratio with age, (2) Decrease in amount of tryptase per mast cell that is being spontaneously secreted, (3) Decreased mast cell mediator releasability due to hormonal changes or antimediator therapy, and (4) Natural course of the disease leading to decrease in total body mast cell burden.

Ongoing Research

A new diagnostic algorithm for patients with suspected mastocytosis has been recently proposed [99]. Classification of childhood mastocytosis with prognostic implication is needed for future research [7].

Conclusion

In conclusion, pediatric mastocytosis is a heterogeneous group of diseases due to a clonal proliferation of mast cells. Skin-limited disease and a good prognosis are typical. However, some patients may require treatment for mast cell-mediated symptoms or progress to systemic forms of mastocytosis. More research is required to better predict the prognosis of these children.

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Part VII

Acne and Acneiform Conditions

Pediatric and Adolescent Acne

38

Charlene Lam and Andrea L. Zaenglein

Abstract

Acne is one of the most common dermatologic concerns in adolescents of all skin types. The incidence of pediatric acne is also increasing with early onsets of adrenarche, especially in certain ethnic groups. Notably, there are some vital differences in the presentation of acne in children and in patients with skin of color. Despite the increasing awareness of acne in skin of color, research in this population, especially in the pediatric age group, is still sparse. Most recommendations are based on expert opinion and small studies. The principles of acne treatment are the same within age groups and skin types, but creating age-appropriate treatment plans and managing the sequelae of acne, hyperpigmentation and scarring can be the most challenging in skin of color patients.

Keywords

Acne • Neonatal acne • Pediatric acne • Mid-childhood acne • Preadolescent acne • Adolescent acne • Acneiform eruptions • Skin of color • Postinflammatory hyperpigmentation • Scarring • Treatment • Quality of life

Abbreviations

P. acnes	*Propionibacterium acnes*
DHEAS	Dehydroepiandrosterone sulfate
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
PCOS	Polycystic ovary syndrome
SAPHO	Synovitis, arthritis/acne, palmar pustulosis, hyperostosis, osteitis
PIH	Postinflammatory hyperpigmentation
EDCs	Endocrine-disrupting chemicals
BP	Benzoyl peroxide
SA	Salicylic acid
AA	Azelaic acid
CP	Clindamycin phosphate
DHS	Drug hypersensitivity
LLS	Lupus-like syndrome
COCs	Combined oral contraceptives
SHBG	Steroid hormone binding globulin
DHT	Dihydrotestosterone
STIs	Sexually transmitted infections
DMPA	Depot medroxyprogesterone acetate
LARC	Long-acting reversible contraception
DISH	Diffuse idiopathic skeletal hyperostosis
IBD	Inflammatory bowel disease
IPL	Intense pulse light
POMC	Pro-opiomelanocortin
PDT	Photodynamic therapy
LPDL	Long-pulsed dye laser

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Background

1. Acne vulgaris is one of the most common dermatologic complaints in adolescents of all skin colors.
2. The pathogenesis of acne is similar in all skin types.
3. There are some key differences in the presentation and management of pediatric acne, especially in children with skin of color.

Acne is not a unique condition in children and adolescents with skin of color; however, there are special considerations when treating acne in this population.

The epidemiology of acne in skin of color is relatively unknown [1]. There is a paucity of data regarding frequency in different ethnic groups. With the available evidence, acne appears to affect all ethnicities with a few notable exceptions (see below). It is the most common dermatologic complaint for which Caucasian, Hispanic, and African-American patients seek dermatologic help and the second most common skin concern in Asian patients [2]. In an epidemiologic, cross-sectional study comparing acne vulgaris in Caucasian, Asian, Continental Indian, and African-American women, the prevalence of acne was more common in African Americans and Hispanics compared to Asians and Continental Indians [3]. Another self-reported questionnaire study found that white adolescents between 10 and 19 years had an increased risk of developing acne compared to blacks, Asians, and Hispanics [4]. Other studies have demonstrated a similar prevalence and incidence of acne between white and blacks, while others have found some slight differences [1]. In a cross-sectional study in Peru, the prevalence of acne was higher among whites (44 %) and Mestizos (43 %) compared to Indians (28 %) [5]. Another cross-sectional study of 539 Nigerian subjects aged 11–19 years found the prevalence of acne was 90.7 %, although most were classified as mild [6].

Cultural differences in perceptions and understanding of acne may also affect data regarding the prevalence. Asians tend to view acne as a rite of passage into adulthood and believe that it will resolve with time [7]. This may contribute to the percentage of patients seeking professional help. However, a cross-sectional study in a New Jersey middle and high school did not find a difference between Asians and whites seeking medical help for acne [4]. This may be due to the influence of westernized views of acne in Asian Americans.

Traditionally, acne vulgaris is one of the first markers of puberty, occurring with the onset of adrenarche, in females at 12–13 years and males at 14–15 years. There is a trend towards increasing prevalence of acne among younger children [8]. This may be due to the earlier onset of puberty in American children [9–11]. Furthermore, puberty, including menarche, is seen earlier in African Americans than in Caucasians and Hispanics [12–16]. The earlier onset of acne can have treatment implications as traditionally studies have been done on older populations [17].

Pathogenesis

With our current understanding, the pathogenesis of acne appears to be the same for all ethnicities. The development of acne is centered on the pilosebaceous unit [18]. The four main factors involved in the pathogenesis of acne include (1) follicular epidermal hyperproliferation, (2) inflammation, (3) concentration and activity of *Propionibacterium acnes* (*P. acnes*), and (4) excess sebum production [19].

There are no studies examining the racial differences in the pilosebaceous follicle or its hyperkeratinization. One study showed that black skin has more layers in the stratum corneum and is less permeable [20]. Given the limited number of patients and no follow-up studies to further demonstrate this finding, no conclusions can be made. Differences in *P. acnes* have not been statistically determined [21].

Increased sebum production and excretion is associated with the development of acne. During adolescence, adrenal and gonadal androgen levels are elevated which stimulates sebum production. There is controversy regarding the differences in sebum production and sebaceous gland size between different skin types, with most studies showing no differences in sebum production between black and white subjects [22–24].

A popular theory on the causation of acne is the westernized diet [25]. This hypothesis stems from an observation of two indigenous cultures where acne was nonexistent [26]. The authors concluded that environmental factors such as diet may play a major role in the prevalence of acne in Western societies [25]. Additionally, a pilot study on overweight Australian males demonstrated a low glycemic diet improved acne [27]. However, more rigorous studies are needed to evaluate the role of diet before conclusions can be drawn.

Clinical Presentation

1. Acne vulgaris presents similarly in all skin types; however, darker skin color may mask inflammation and disguise active disease.
2. Postinflammatory hyperpigmentation and scarring/keloid formation may be the main concern for skin of color patients.
3. There are special considerations in ethnic populations, such as hair care practices, use of skin-lightening products, and previous problems with scarring.

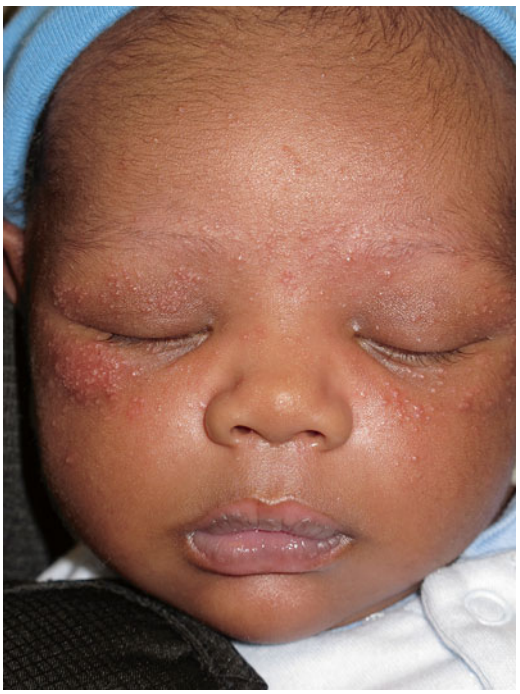

Fig. 38.1 Neonatal acne consisting of small pinkish-red inflamed papules and pustules mostly confined to the cheeks, eyelids, and forehead

Although often considered a teenage ailment, acne and acneiform conditions can occur in all ages. Acne during different age groups may present with different concerns.

Neonatal Acne

Neonatal acne (acne neonatorum, neonatal cephalic pustulosis) is a very common disorder, affecting about 20 % of all newborns [28]. It typically presents during the first 2–3 months of life, lasting several weeks. No ethnic differences are noted.

Clinically, multiple, small, pinkish-red inflamed papules and pustules predominate. Lesions are confined to the cheeks, chin, eyelids, and forehead (Fig. 38.1). Occasionally, involvement of the chest and upper back is seen. When comedones or acneiform nodules are present, a diagnosis of infantile acne should be considered and treated accordingly. Mild postinflammatory hyperpigmentation, but not scarring, may be observed as the lesions resolve.

The pathogenesis of neonatal acne is unclear. Sebum production and *Malassezia* species have been implicated, but, their exact role has not been clarified [29].

The condition is usually mild and always self-limited. Typically, reassurance is all that is needed. In more extensive cases, treatment with ketoconazole 2 % cream can improve the eruption [30].

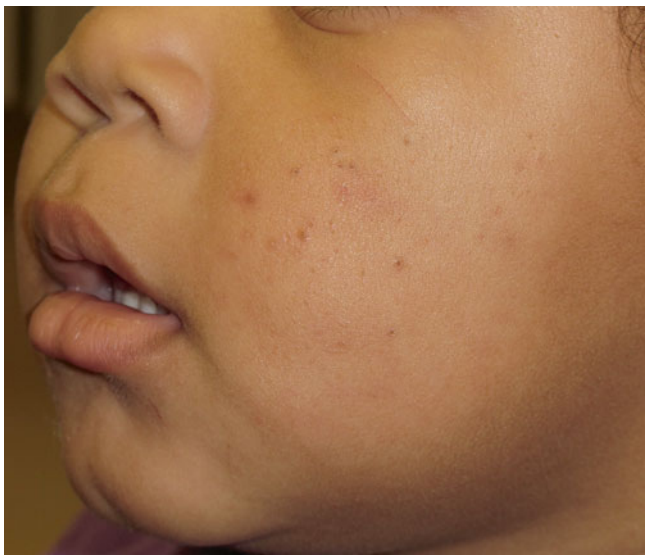

Fig. 38.2 Infantile acne consisting mostly of open comedones scattered over the cheeks

Infantile Acne

Infantile acne typically appears around 6 months of age and may last 1–2 years. Boys are more frequently affected than girls. Clinically, infants present with classic acne lesions: open and closed comedones, inflammatory papules, and small pustules (Fig. 38.2). Uncommonly, severe nodular acne may be seen [31]. Small, pitted scars are commonly observed sequelae of infantile acne, occurring in up to 50 % of affected infants [32]. Parents may be counseled that infantile acne is associated with a strong family history of acne and may be associated with more severe adolescent acne [33].

The pathogenesis of infantile acne is due to the transient overproduction of androgens by the developing adrenal gland. Increased dehydroepiandrosterone sulfate (DHEAS) is noted, with an increased production of testicular androgens in boys as well [33]. The majority of cases are not the result of clinically significant hormonal abnormities. However, a thorough physical examination including growth (height, weight, and growth curve), testicular growth and breast development, presence of hirsutism, and increased muscle mass should be done. If signs of precocious puberty are noted, a hormonal work-up should be undertaken [31, 34]. Serologic evaluation should include follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, DHEAS, 17-OH-progesterone, serum cortisol, thyroid studies, and a bone age [31].

Treatment involves gentle, "baby friendly" formulations of topical retinoids (adapalene 0.1 % gel or tretinoin 0.025 % cream) and topical antimicrobials (benzoyl peroxide 2.5 % cream). Washes and alcohol-based gels should be avoided.

An open-label trial of adapalene 0.1 % gel in 12 patients with infantile acne demonstrated a reduction of inflammatory and noninflammatory lesions in 4 months [35]. Side effects were mild and did not require discontinuation of the medication. At 1-year follow-up, there was no observable scarring [35]. Oral antibiotics appropriate for babies, such as erythromycin or azithromycin, are used for moderate-to-severe cases and oral isotretinoin may be considered for the very rare cases of severe nodular disease [31].

Mid-Childhood Acne

Mid-childhood acne, defined as acne occurring in children aged 1–7 years, is rare [31]. At this age, children should not produce significant levels of adrenal or gonadal androgens; therefore, an endocrine abnormality should be suspected in any child presenting with acne during this time frame. A thorough physical examination, evaluating for signs of precocious puberty, should be performed. A referral to a pediatric endocrinology is usually warranted to rule out adrenal or gonadal pathology such as androgen-secreting tumors as well as evaluating for other causes of precocious puberty. Congenital adrenal hyperplasia is more common in some groups with skin of color such as Hispanics and atypical cases may not have been noted in infancy [36]. Early adrenarche can be also seen in girls at risk for polycystic ovarian syndrome (PCOS). With a negative work-up, treatment is similar to adolescent acne (see below) with the exception of oral tetracycline and doxycycline which are contraindicated in those 8 years and younger due to risk of bone and dental enamel damage [31]. Minocycline is not approved for use in children less than 12 years of age.

Preadolescent Acne

Acne in the preadolescent period (ages 7–11) is a not uncommon, and the incidence appears to be on the rise [17, 29, 31]. Early acne presents as mostly comedones in the T-zone, involving the forehead and central face with occasional inflammatory papules (Figs. 38.3 and 38.4) [31]. Comedones can also appear in the concha bowl of the ear. In girls of any ethnicity, an early onset of acne (<10 years of age) may be indication of more severe adolescent acne [37]. If there are signs of androgen excess, then the appropriate work-up should be done. PCOS is important to consider in severe acne and/or that recalcitrant to treatment. Screening questions regarding irregular menstrual cycles, excessive premenstrual symptoms, and hirsutism may guide management. Treatment is similar to adolescent acne with an emphasis on simplifying treatment plans to aid with adherence. While limited, there are some therapeutic trials in this younger age group [38–40]. These are discussed below.

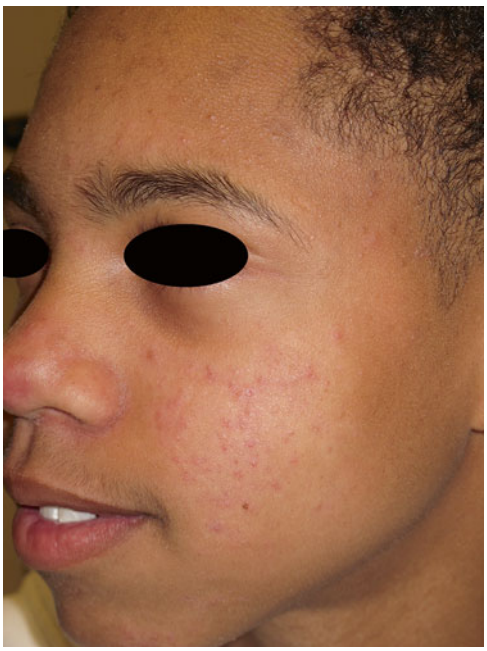

Fig. 38.3 Preadolescent acne consisting mostly of closed comedones and small pink papules

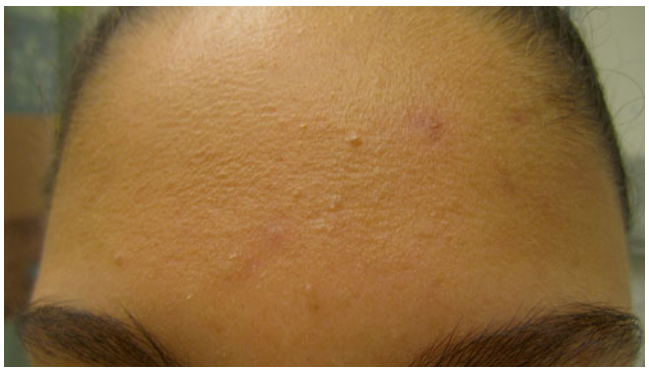

Fig. 38.4 Preadolescent acne concentrated in the "T-zone" area of forehead

Adolescent Acne

As mentioned above, acne is one of the most common disorders of adolescence in all ethnic backgrounds. There are limited studies comparing the differences in acne characteristics between differing skin types. Some studies have indicated that Caucasians and Hispanics are more prone to nodulocystic acne than African Americans [41, 42].

The diagnosis of acne is usually straightforward and made clinically by the presence of classic acne lesions: open and closed comedones (Fig. 38.5), inflammatory papules and pustules (Fig. 38.6), and nodules in more severe disease. These lesion types are present in all skin tones. However, erythema may be more challenging to appreciate in darker skin tones and may appear dark, resembling postinflammatory

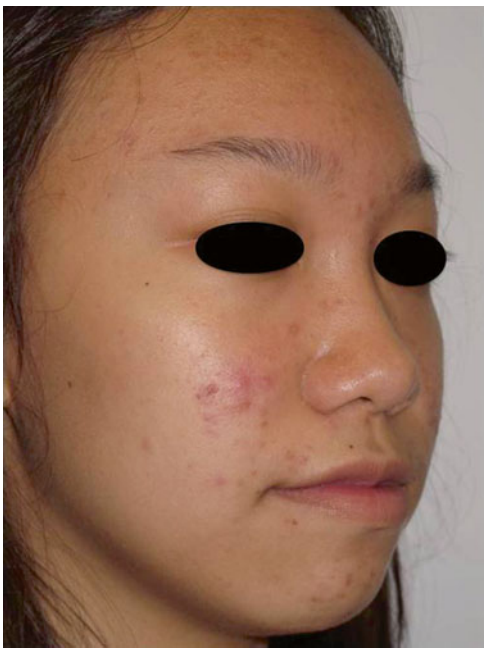

Fig. 38.5 Adolescent acne in an Asian female demonstrating moderate inflammatory and comedonal acne

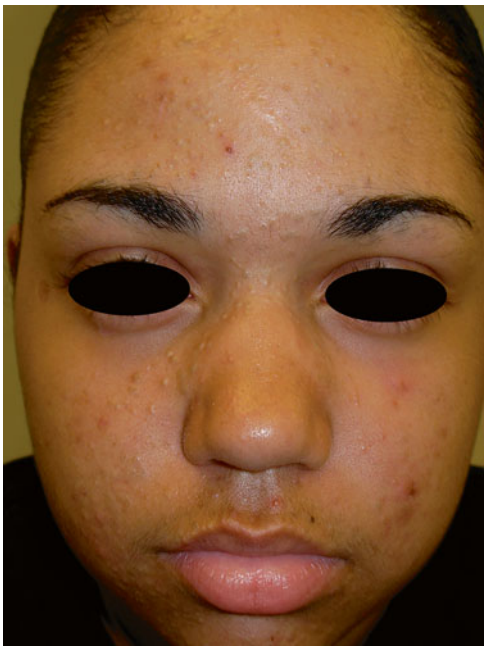

Fig. 38.6 Deep comedonal acne in an adolescent

hyperpigmentation. To help differentiate, active lesions may be palpated for induration or tenderness [43].

A differential must be considered especially when traditional treatments are not effective [44]. The differential includes gram-negative folliculitis, pityrosporum folliculitis [45], steroid-induced acne, keratosis pilaris, eruptive hidradenoma, molluscum contagiosum, pseudofolliculitis barbae, acne keloidalis nuchae [46], and hidradenitis suppurativa. Additionally, it

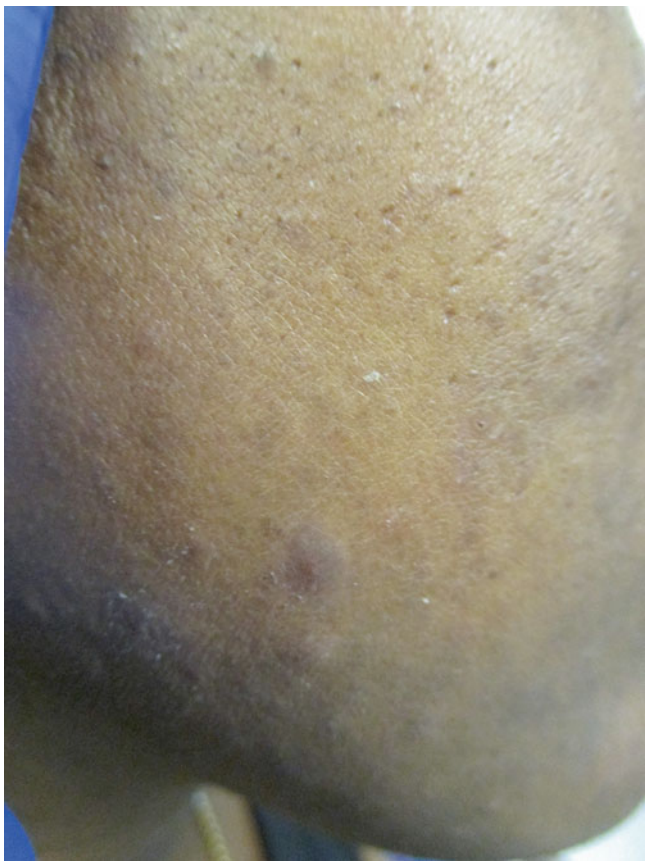

Fig. 38.7 Sequelae—Postinflammatory hyperpigmentation

is important to evaluate for any systemic hormonal abnormalities that may cause acne such as PCOS, hormone-secreting tumors, or autoinflammatory disorder such as SAPHO (synovitis, arthritis/acne, palmar pustulosis, hyperostosis, osteitis).

Sequelae

The sequelae of acne are a crucial consideration when considering a treatment regimen in skin of color patients. Postinflammatory hyperpigmentation (PIH) and hypertrophic/atrophic scarring or keloid formation can result.

PIH is characterized by hyperpigmented macules or patches that can occur at sites of acne or result from irritation caused by acne treatment. Often, PIH secondary to acne may be the chief complaint at presentation (Fig. 38.7) [47]. African Americans (65 %) and Hispanics (48 %) have a higher prevalence of PIH than Asians (18 %), Continental Indians (10 %), and Caucasians (25 %) [3, 41]. Although African Americans may experience less severe nodular acne, their acne may have a higher degree of inflammation when evaluated histologically [48, 49], thus contributing to the propensity for PIH [50]. In general, when the pigment is within the epidermis, it appears lighter and better circumscribed (epidermal melanosis). When the pigment is in the

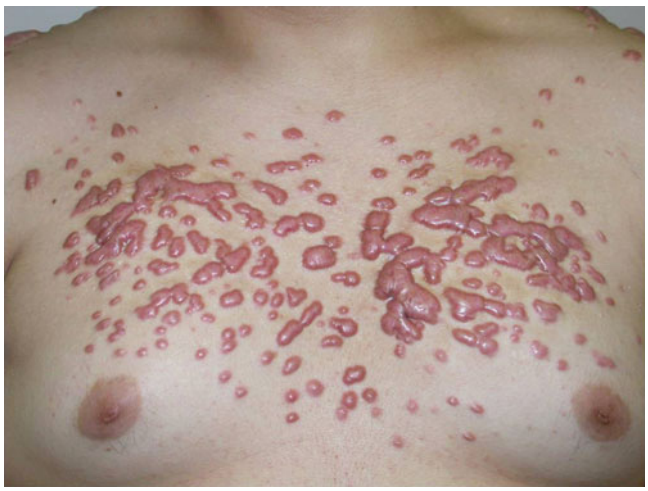

Fig. 38.8 Sequelae—Extensive keloids due to acne fulminans in an adolescent

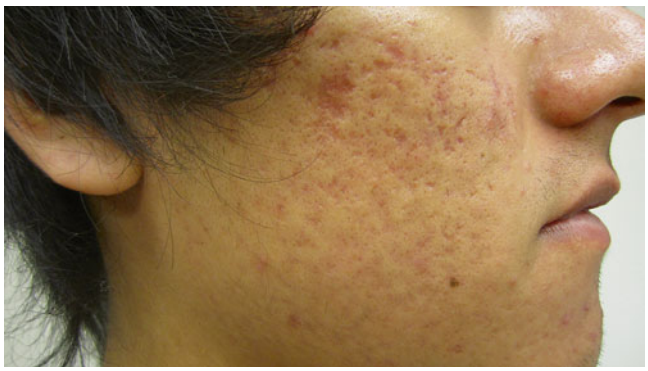

Fig. 38.9 Sequelae—Atrophic scarring due to nodulocystic acne

dermis, it appears darker gray and less demarcated [51]. PIH can cause significant stress and frustration as dermal hyperpigmentation and epidermal melanosis may take years and 6–12 months to fade, respectively [52].

Keloids (Fig. 38.8) and hypertrophic/atrophic (Figs. 38.9 and 38.10) scarring formation occur between 5 and 16 times more often in skin of color, and can result in significant and permanent disfigurement [50]. Pain and itching are common symptoms. The biologic basis of keloidal/hypertrophic scarring has been widely explored. There are multiple contributing factors such as differences in fibroblast size and activity, immune cell action, and growth factors that result in the promotion of excess collagen and inhibition of extracellular matrix degradation [53, 54]. Treatment of keloids is exceptionally challenging and often unsuccessful.

Special Considerations

It is important to inquire about topical beauty products used in all patients, but it is especially crucial in those with skin of color. There are different perceptions of acne and beauty and

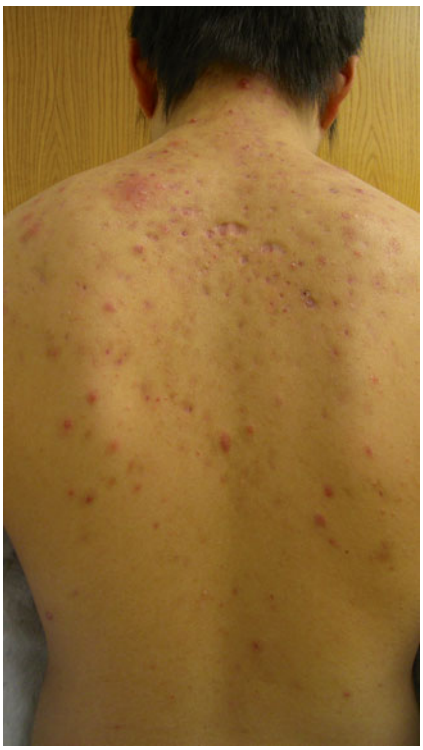

Fig. 38.10 Mixture of inflammatory acne and atrophic scarring

subsequent practices range widely among different groups. It is impossible to generalize for each group, but hair care practices, cultural remedies, and over-the-counter treatments can play a major role in acneiform eruptions [7]. For example, one study examining practices in Arab Americans found patients used mixtures of honey and sugar to exfoliate, lemon juice or a milk and honey blend to wash the face, and mixture of herbs and Dead Sea clay to make facial masks [55]. Cocoa butter is also a popular product among African Americans and can be comedogenic [56].

Furthermore, astringents, scrubs, buffs, toners, and sonic brushes are used regardless of background or skin type. The goal of facial cleansing is to remove makeup, dirt, and excess oil [57]. Excessive and harsh cleansing routines predispose one to increased transepidermal water loss, bacterial colonization, and comedone formation, and can result in inflammation [58, 59]. This is especially problematic in those with skin of color as increased erythema and irritation can cause PIH.

Hair Care Practices

Africans, Afro-Caribbeans, and African Americans often use hair pomades to improve texture, assist in manageability, and reduce brittleness of hair [26, 41, 56, 60]. A survey of patients at a skin of color clinic found 46 % of patients used

hair oil or pomades and 70 % of these patients had forehead acne [41]. Hair pomades and oils often contain lanolin, coconut oil, squalene, mineral oil, and isopropyl myristate which are known to be comedogenic. These result in a monomorphic acne called *pomade acne* [60]. There is even one study that suggests that use of hair oils may contribute to early menarche [61]. The authors speculate that hair oils often contain placenta, estrogen, and endocrine-disrupting chemicals (EDCs), such as mono-ethyl phthalate or methylparaben that may accelerate puberty [61]. Further studies on the hormonal effects of these substances are needed. However, inquiring about hair products is essential, and recommending silicone or water-based gels as alternatives can prevent this type of acne [26, 56].

Skin-Lightening Practices

The use of skin beaching agents is common in skin of color [41]. Beauty stores that specialize in African, Afro-Caribbean [62], African-American, and Asian products frequently have aisles containing products devoted to skin lightening, demonstrating its popularity [43, 53]. Many of these products are imported and contain potent corticosteroids such as clobetasol propionate and are sold under the names of Dermovate, Betnovate, Topsone, and Movate. It is also common for patients to obtain products while traveling abroad, or from friends and family members visiting the United States. In a dermatology clinic in Dakar, Senegal, over half the women were current users of bleaching products. Products used contained hydroquinone (4–8.7 %), corticosteroids (usually class I), mercury iodide, and other caustic agents [63]. These products can result in *steroid-induced acne* [46, 63] (Fig. 38.11) and cause other problems such as skin atrophy, hypopigmentation, erythema, and telangiectases. A prospective study in Lome, Togo examined acne in patients who were bleaching their skin, and found the main areas for acne lesions were on the back and shoulders [64]. There are also increased rates of steroid-induced acne in India and Hong Kong due to lax regulation on topical steroids and widespread use [7].

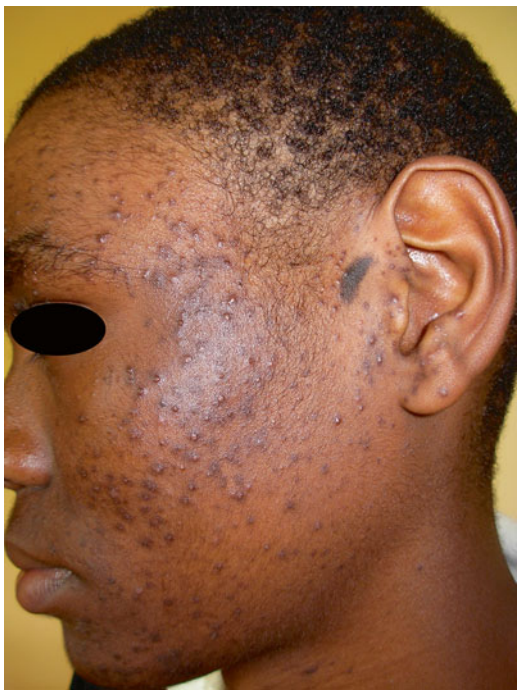

Fig. 38.11 17-year-old Tanzanian male with steroid-induced acne due to over-the-counter clobetasol used for skin bleaching

Treatment

1. Treatment is two-part: controlling the acne and then managing its sequelae.
2. Treat acne in skin of color early and aggressively to prevent long-term side effects: postinflammatory hyperpigmentation, hypertrophic/atrophic scarring, and keloids.
3. Tailor treatment strategies (age, medication tolerance, risk of scarring) towards individual skin type.

Treatment of acne in skin of color should be done early and aggressively to prevent PIH and scarring. There are published acne treatment guidelines for both children and adolescents [31, 65]. Modified guidelines for Asian patients [7] can be applicable to all skin of color patients [26]. Therapy should be carefully tailored to treat acne without inducing too much irritation that will result in PIH. The main difference in treating acne in darker skin tones is that treatment is not over after the acne is under control. The second stage of treatment addresses the aftermath of acne.

With the multifactorial components of acne pathogenesis, current acne therapies target individual factors contributing to acne formation. Ideally, treatment regimens combine therapies to address multiple pathogenic factors simultaneously. Patient expectations need to be managed; allowing them to understand effectiveness may not be appreciated for 8–12 weeks. Table 38.1 provides a treatment algorithm based on severity.

Topicals

Retinoids, used as monotherapy and in combination, are the cornerstone of treatment in acne (Table 38.2). It can be especially useful in skin of color as it can help with PIH as well (see below). Large studies including adolescent populations

Table 38.1 Treatment algorithm for acne in skin of color

	Mild		Moderate		Severe
	Comedonal	Papular/Pustular	Papular/Pustular	Nodular	Nodular
First choice	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid ± BP	Oral antibiotic + retinoid + BP	Oral isotretinoin
Alternatives	Alt. topical retinoid or azelaic acid or salicylic acid	Alt. topical retinoid antimicrobial agent + alt. topical retinoid or azelaic acid	Alt. oral antibiotic + alt. topical retinoid ± BP	Oral isotretinoin or alt. oral antibiotic + alt. oral topical retinoid ± BP/azelaic acid	High dose oral antibiotic + topical retinoid + BP
Alternatives for females	See first choice	See first choice	Oral antiandrogen + topical retinoid/azelaic acid ± topical antimicrobial	Oral antiandrogen + topical retinoid/± oral antibiotic ± alt. antimicrobial	High dose oral antiandrogen + topical retinoid ± alt. topical antimicrobial
Maintenance therapy	Topical retinoid		Topical retinoid ± BP		
Postinflammatory hyperpigmentation	4 % Hydroquinone "Spot Treatment"		5–10 % Hydroquinone ± Chemical peels, Microdermabrasion, Lasers		

Adapted from Gollnick et al. [63] and Callender [50]
BP benzoyl peroxide

Table 38.2 Frequently used topical retinoids and fixed-combination agents

		Formulations	Comments
Retinoids	Tretinoin		
	Generic	0.025, 0.05, 0.1 % cream 0.01, 0.025 % gel	Pregnancy category C
	Atralin® (Coria Laboratories, Fort Worth, TX)	0.05 % aqueous gel	Contraindicated with fish allergies [26]
	Retin-A Micro® (OrthoNeutrogena, Los Angeles, CA)	0.04, 0.1 %	Microsphere gel or gel pump
	Tretin-X® (Triax Pharmaceuticals, Cranford, NJ)	0.025, 0.05, 0.1 % cream 0.01, 0.025 % gel	
	Ziana® (Medicis, Scottsdale, AZ)	Tretinoin 0.025 % Clindamycin phosphate 1.2 % gel	
	Adapalene		
	Differin® (Galderma Laboratories, Fort Worth, TX)	0.1 % cream 0.1, 0.3 % gel 0.1 % solution 0.1 % lotion	
	Epiduo® (Galderma Laboratories, Fort Worth, TX)	Adapalene 0.1 % BP 2.5 % gel	FDA approved for 9–11 years of age
	Tazarotene		
	Tazorac® (Allergan, Irvine, CA)	0.05, 0.1 % cream 0.05, 0.1 % gel	Second-line treatment in skin of color Pregnancy category X
Antibiotic and BP	Benzamycin	Erythromycin 3 % BP 5 % gel	Requires refrigeration
	Benzaclin	Clindamycin 1 % BP 5 % gel	
	Duac® (Steifel Laboratories, Coral Gables, FL)	Clindamycin 1 % BP 5 % gel	
	Acanya® (Coria Laboratories, Fort Worth, TX)	Clindamycin phosphate 1.2 % gel BP 2.5 % gel	

Adapted from Davis and Callender [43] and Eichenfield et al. [31]
BP benzoyl peroxide

of 12–18 years of age have demonstrated effectiveness and safety of retinoids. Two products are currently FDA approved for patients aged 9–11: tretinoin gel 0.05 % (Atralin®, Coria Laboratories, Fort Worth, TX) for patients ≥ 10 years of age [66] and adapalene/benzoyl peroxide gel 0.1 %/2.5 % (Epiduo®, Galderma Laboratories, Fort Worth, TX) for patients ≥ 9 years of age [67]. However, other retinoids such as adapalene, tretinoin gel, and tretinoin microsphere gel have documented safety in patients less than 12 years of age [35, 38, 68].

Retinoids normalize follicular epithelium desquamation, preventing microcomedone formation and clearing existing comedones [69]. Some retinoids also have anti-inflammatory effects [70]. Appropriate use involves a pea-size amount to entire face. Emphasize to patients that it is not a spot treatment as there is a tendency to use it as such, resulting in inflammation and PIH. Common side effects include burning, stinging, dryness, and scaling [65]. There is a perception amongst those treating Asians that they may have more sensitive skin and their acne may respond to retinoids slower than Caucasian patients [7]. To improve tolerability, initiate retinoid at the lowest strength, avoid alcohol-based vehicles, encourage moisturizer use, and start with thrice-weekly application and increase to daily as tolerated [31, 38, 71]. Conversely, if patients have oily skin and little risk for irritation, stronger retinoids and gel formulations can be utilized [41]. Adapalene is a distinct second-generation retinoid that is considered well tolerated. It is photostable and can be combined with benzoyl peroxide [72].

Preadolescent and Skin of Color Trials

Although there are no studies to date focusing on preadolescents or children with skin of color in acne, understanding the existing data on preadolescents and attempting extract the data on the skin of color population may provide insight into treatment recommendations. Both efficacy and tolerability are important considerations in this population.

Micronized gel formulations have been used to increase tolerability. In a 12-week open-label study of 40 patients (8–12 years of age) using microsphere tretinoin 0.04 % gel daily, 75 % of participants were graded as mild or clear by the end of 12 weeks [38]. In this study, 62.5 % (25/40) of the patients had skin of color (black, Hispanic, Asian, or combination with white) [38]. Of all the participants, 30 % experienced irritation although it was graded as mild and no one was discontinued from the drug due to irritation. Interestingly, 5 % ($n=2$) experienced PIH.

In a randomized, controlled study of microsphere tretinoin gel 0.04 % pump in preadolescents [9–11], there was a significant improvement in noninflammatory lesions in the treatment group versus the vehicle by 12 weeks (−19.9 vs. −9.7, $p=0.04$) and overall improvement in the investigator global assessment as well. However, there was no difference in the two investigator global evaluations of acne severity scales: a pediatric scale and standard 5-point FDA scale, which may have been due to the small sample size [39]. Of the 55 patients receiving treatment, 24 were skin of color (African-American—12; Hispanic—10; Asian—2), and in the vehicle group, 17 were skin of color (African-American—8; Hispanic—9; Asian—0) [39]. Although the results were not subdivided by race, there were no statistically significant changes in baseline erythema, dryness, peeling, burning or stinging, or itching between treatment and vehicle by week 12. However, 15 (27.3 %) patients with treatment did cite skin irritation as an adverse effect and four patients on treatment discontinued the trial compared to the one on vehicle.

Adapalene has been shown to be well tolerated in skin of color [71, 73–75]. A meta-analysis of five studies evaluating the safety and efficacy of adapalene use in black patients (Fitzpatrick skin types IV–VI) compared to white patients demonstrated comparable effectiveness. Blacks were less likely to have erythema, scaling, and moderate-to-severe dryness [73]. A randomized, blinded controlled study evaluating the effectiveness and safety of adapalene 0.1 % gel in 200 Japanese patients aged 12–35 (only 2 patients were between the age of 12 and 15 and 16 patients were aged 16–19 years) demonstrated reduction in inflammatory and noninflammatory lesions [71]. Most of the side effects were mild to moderate and noted during the first 2 weeks of treatment, subsiding as treatment continued [71]. A study comparing adapalene gel 0.1 % and tretinoin gel 0.025 % in Chinese patients ($n=139$) found adapalene comparable in efficacy but less irritating than tretinoin [76].

Tazarotene is another effective retinoid but is not approved in the United States for children less than 12 years. There is no specific data on tazarotene in adolescents with skin of color. An open-label study on tazarotene 0.1 % gel in Indian patients ($n=126$) aged 13–30 showed moderate to complete clearance in 90 % of inflammatory and noninflammatory acne by weeks 8 and 12 [77].

Topical Antimicrobials

Benzoyl peroxide (BP) is an effective and safe treatment for acne in all age groups [78]. Its lipophilic nature allows it to penetrate the stratum corneum and into the pilosebaceous gland where *P. acnes* are located. It then generates free radicals, oxidizing the proteins in the cell walls of *P. acnes*. It also has mild comedolytic and anti-inflammatory properties [79, 80]. Other positive qualities of BP include prevention of antibiotic resistance in *P. acnes* and increased efficacy

in combination with retinoids [81, 82]. There have been no reports of *P. acnes* resistance to BP [83–85].

Side effects of BP include dryness, erythema, and flaking during initiation of treatment. Lower concentrations of BP can decrease irritation without reducing effectiveness [31]. Allergic contact dermatitis can occur in 1/500 people. Complaints of pruritus and eye swelling can be indicators. Patients can conduct a "use test" to distinguish between irritation and allergy [86].

BP formulations range from 2.5 to 10 %. One study demonstrated that treatment of acne on the back may benefit from an increased concentration and longer contact time [87]. BP leave-on products can leave a white film, which can be more apparent in skin of color. Therefore, BP washes may garner improved compliance, though they do require a 20-s contact time to achieve effectiveness. Additionally, washes can reduce the possibility of bleaching clothing, bedding, and towels.

Salicylic acid (SA) is frequently found in over-the-counter acne treatments and is generally well tolerated. It has anti-comedolytic and anti-inflammatory properties. However, in a study comparing SA wash with BP wash, SA was less effective [88].

Topical erythromycin and clindamycin have been used for decades in the treatment of acne and are also generally well tolerated. They are typically used in combination with BP to decrease the development of bacterial resistance. There are rare reports of topical clindamycin associated with pseudomembranous colitis [89, 90]. Topical sulfacetamide is more widely used in rosacea and its odor may limit its use. Patients with sulfa allergies should avoid this product.

Azelaic acid (AA), a dicarboxylic acid produced by *Pityrosporum ovale*, has antibacterial, anti-inflammatory, and anti-comedogenic properties. Additionally, it has been found to improve PIH (see below). It is formulated in a 15 % gel and 20 % cream. Although well tolerated, mild burning, tingling, and pruritus are not uncommon. Studies have demonstrated its efficacy to be comparable to tretinoin 0.05 % cream, BP 5 % gel, clindamycin 1 %, and erythromycin 2 % ointment [91, 92]. Its efficacy is thought to increase with the combination with a retinoid or BP.

Topical dapsone is a synthetic sulfone that has antimicrobial and anti-inflammatory effects. However its mechanism of action in acne is unknown. Two 12-week randomized, double-blind trials comparing topical dapsone 5 % gel twice daily with vehicle gel in patients aged 12 years and older found a significant reduction in inflammatory and noninflammatory lesions [93]. Initial concerns related to hematologic safety in individuals (≥12 years of age) with glucose-6-phosphate dehydrogenase deficiency were unfounded with application on face, neck, and upper shoulders [94]. However, widespread use over large areas in children aged 6–10 in at-risk populations is cautioned [26]. When dapsone and BP are used together, it can result in a temporary orange discoloration of the skin or hair [31].

Combination Topical Products

Combination topical products can be extremely beneficial for adherence especially in a younger population (Table 38.2). In a post hoc analysis of 2 double-blind, multicenter studies, 1,755 adolescents ranging from 12 to <18 years with moderate-to-severe acne were randomized to receive either a fixed combination of clindamycin phosphate (CP) 1.2 %–benzoyl peroxide (BP) 2.5 % gel, CP 1.2 % alone, BP 2.5 % alone, or vehicle once daily for 12 weeks. There was a statistically significantly reduction in inflammatory and noninflammatory lesions in the CP 1.2 %–BP 2.5 % gel group versus the other 3 groups [95]. When the skin of color group ($n=337$) from this study was evaluated, similar lesion count reductions were noted between skin of color and the non-skin of color control [68]. Topical BP 5 %–erythromycin 3 % combination gel has long been available. However it does require refrigeration, which may curtail compliance. One 12-week randomized, placebo-controlled, double-blind trial of 36 patients revealed that CP 1.2 %–tretinoin 0.025 % combination gel in skin types IV–VI had a mild reduction of inflammatory lesions compared to the placebo and no change in PIH. However, it was relatively well tolerated [96].

Most recently, a randomized 12-week study compared pre-adolescents aged 9–11 using topical adapalene–BP (Epiduo®, Galderma Laboratories, Fort Worth, Texas) ($n=142$) to a vehicle ($n=143$). It found adapalene–BP was significantly superior to vehicle with regard to treatment success (49.3 % vs. 15.9 %) and percentage of reduction in total lesion count (68.6 % vs. 19.3 %), inflammatory (63.2 vs. 14.3 %), and noninflammatory lesion counts (70.7 % vs. 14.6) all ($p<0.001$). Overall, it was well tolerated. Only 2 subjects discontinued in the adapalene–BP group due to erythema and skin irritation, both mild in severity [40]. Along with this data and that of 285 patients aged 9–11 years from Galderma, the FDA approved this combination product for use in those 9 years old and older [97].

Oral Antibiotics

Oral antibiotics are very effective in treating moderate-to-severe acne (Table 38.3). It is important to counsel patients that 6–8 weeks of treatment is required to see improvement and the goal is to taper oral antibiotics once disease is diminished. Combination therapy, with topical retinoids and antimicrobials, is required to ensure best results and to decrease the risk of antibiotic resistance. For older children and adolescents, the tetracycline class of antibiotics is most frequently used including doxycycline, minocycline, and tetracycline. Although a mainstay of acne treatment, with the exception of extended-release minocycline, there is no FDA approval for oral antibiotics in acne [98].

Table 38.3 Oral antibiotics used for pediatric acne

	Antibiotic	Recommended dosage	Comments/side-effects
Frequently used	Tetracycline	250–500 mg BID	Dental staining <9 years
			Ingest on empty stomach preferable; dairy products and iron, calcium, or many other metal ions found in vitamins/supplements decrease absorption
			GI upset, photosensitivity, teratogenic, PTC, VVC, FDE
	Minocycline	50–100 mg QD-BID	Dental staining <9 years
			Dairy products decrease absorption
			Acute: Vertigo, GI upset (less than doxycycline), teratogenic, PTC, VVC
			Chronic: LLS, blue-gray hyperpigmentation, hepatitis
		ER 1 mg/kg QD	Lower incidence of vestibular and pigmentation side effects with ER formulations
	Doxycycline	50–100 mg QD-BID	Dental staining <9 years
		ER 75, 100, 150 mg QD	Can be taken with meals; take with large glass of water and maintain upright position ≥1 h to decrease risk of GI upset
			Photosensitivity, photo-onycholysis, teratogenic, PTC, VVC
	Erythromycin	250–500 mg	Antibiotic of choice for children<8 years of age
		Erythromycin ethylsuccinate 400 mg/5 mL, 200 mg/5 mL	High prevalence of antibiotic-resistant *P. acnes*
Less frequently used	Trimethoprim-sulfamethoxazole	80/400 mg, 160/800 mg BID	Severe drug reactions, bone marrow suppression, hepatitis, GI upset, VVC, FDE
			Do not use as first- or second-line agent for acne
	Clindamycin	75–150 mg BID	Pseudomembranous colitis, GI upset, drug reactions, VVC
	Cephalexin	250–500 mg BID	GI upset, drug reactions, VVC
		125 mg/5 mL, 250 mg/5 mL	

Adapted from Eichenfield et al. [31] and Paller and Mancini [192]
GI gastrointestinal, *PTC* pseudotumor cerebri, *VVC* vulvovaginal candidiasis, *ER* extended-release formulation, *FDE* fixed drug eruption, *LLS* lupus-like syndrome, *P. acnes Propionibacterium acnes*

Macrolides

For children under 8 years of age, kids who have not lost their primary teeth, and those with tetracycline allergies, erythromycin and azithromycin can be used in the treatment of acne. Due to the emergence and prevalence of *P. acnes* resistance to erythromycin, it is not commonly used in older children, except when the tetracyclines are contraindicated [99, 100].

Trimethoprim/Sulfamethoxazole

Trimethoprim/sulfamethoxazole should be used with caution in acne and only in refractory cases due to the risk of severe adverse effects such as Stevens–Johnson syndrome. Data supporting its use in acne are lacking.

Doxycycline

The most common side effects of doxycycline include photosensitivity/phototoxicity and "pill esophagitis" [101–103]. Patients should be instructed to practice good sun protective behaviors. To prevent esophagitis, patients should take doxycycline with food, or with a large glass of water, and remain in an upright position for at least 2 h after ingestion. Enteric-coated doxycycline is an alternative form if needed.

Minocycline

Minocycline has less potential for photosensitivity and gastrointestinal discomfort and is frequently used in the management of adolescent acne. Rare and serious side effects should be discussed with patients. Vestibular toxicity, drug hypersensitivity (DHS), and serum sickness-like reaction can occur within days to weeks of initiating the drug. Vestibular toxicity presents with vertigo and/or dizziness and resolves with discontinuation of minocycline [104–106]. DHS usually presents within the first 8 weeks of treatment with flu-like symptoms, diffuse erythema, facial edema, cervical lymphadenopathy, and transaminitis. There may be interstitial inflammation of other organs as well [107, 108].

Conversely, lupus-like syndrome (LLS) and hyperpigmentation tend to occur after chronic use of minocycline (months to years). LLS presents with malaise, distal polyarthralgias with or without polyarthritis, and rarely autoimmune hepatitis. The autoimmune antibody profile can be variable. Antinuclear antibodies are usually present, p-ANCA strongly supports the diagnosis, and anti-histone antibodies are not required for diagnosis [31]. Cutaneous and mucosal blue-gray hyperpigmentation can occur in areas of scarring, on the shins, oral mucosa, sclera, and nail beds. Risk is associated with a cumulative exposure [109–111].

As a class, the tetracyclines can cause pseudotumor cerebri, which presents as headaches and transient visual changes with possible nausea and vomiting [112, 113]. It is important to warn patients of these symptoms as persistence can result in permanent vision loss.

Hormonal

Hormonal treatments in acne can be divided into four groups: (1) androgen receptor blockers, (2) ovarian androgen blockers, (3) adrenal androgen production blockers, and (4) enzyme inhibitors. The two most commonly used agents in the United States include spironolactone (androgen receptor blocker) and combined oral contraceptives (COCs) (ovarian androgen blockers). Hormonal treatments should be considered especially in patients who complain of acne in the mandible region, chin, and neck.

Spironolactone is a steroid androgen receptor blocker and can be very helpful in adult female pattern acne [114–117]. It competes with testosterone and dihydrotestosterone (DHT) for androgen receptors on sebaceous glands and reduces the sebocyte proliferation [118]. Its use in pediatric patients may be limited as there is minimal data on its role in adolescent acne and appropriate age of initiation.

COCs can be very effective in treating the hormonal component of acne. COCs contain an estrogen, ethinyl estradiol, and a varying progestin. The estrogen inhibits LH and FSH, which suppress ovulation and ovarian androgen production. This subsequent reduction in androgens results in a decreased activation of androgen receptors at the level of the sebaceous gland. Estrogen also stimulates the production of steroid hormone binding globulin (SHBG) in the liver, which decreases circulating levels of testosterone.

COCs are rarely used as monotherapy for acne. In most instances, patients are already on a combination therapy of topical retinoids, topical BP, and antibiotics. There are several situations where the addition of COCs is appropriate: (1) girls who desire regulation of their menstrual cycle; (2) inadequate response to treatment; (3) acne flares corresponding with menstrual cycles; (4) complaints of oiliness; and (5) contemplation of isotretinoin therapy [119]. Younger patients and parents can initially present with reluctance and anxiety at the suggestion of starting COCs. Emphasizing the hormonal component in the pathophysiology may reduce discomfort. It can also be presented as a stepwise approach to isotretinoin therapy.

There are currently three FDA-approved COCs for the treatment of acne: ethinyl estradiol/norgestimate (Ortho Tri-cylen®, McNeil Janssen Pharmaceuticals, Raritan, NJ) for females ≥ 15 years of age, ethinyl estradiol/norethindrone (Estrostep®, Warner-Chilcott, Rockaway, NJ) for females ≥ 15 years of age, and most recently, ethinyl estradiol/drospirenone (Yaz®, Bayer, Montville, NJ) for females ≤ 14 years of age.

As stated by American College of Obstetricians and Gynecologists (ACOG), pelvic exams are not required prior to oral contraceptive initiation in teenagers. Most recently, ACOG guidelines recommend less frequent cervical screening in general: 3 years after onset of sexual activity or at the age of 21. The decision to prescribe COCs is not determined

by the pelvic exam findings. COCs can be safely prescribed based on careful review of medical history and blood pressure evaluation [120, 121]. While routine well-women exams are advocated, it is acceptable to start COCs with future follow-up with a gynecologist or primary care physician.

Although the risk of thromboembolic events is lower in adolescents, a careful family history is required and smoking is strongly discouraged. Patients are instructed to take their oral contraceptives daily, at approximately the same time each day. Irregular use impedes treatment; in addition, patients may experience unscheduled bleeding and a false sense of contraception security. Patients are encouraged to set an alarm on their cellular devices as a daily reminder to routinely take their pill. If the daily pill is forgotten or missed, patients should take the missed pill as soon as they realize. If one whole day is missed, the patient should take both pills at the same time [119].

Initial bleeding or spotting is normal during the first 3 months of treatment and should resolve after the body adjusts to the new hormonal levels. Other common side effects include nausea, vomiting, weight gain, mood changes, and breast tenderness. Weight gain is often a cited barrier to treatment. However, a recent Cochrane review indicated no large effect of COCs on weight gain, although the current evidence was not adequate [122]. In teenage patients, it is especially important to mention that COCs do not protect against sexually transmitted infections (STIs). If a patient is using COCs for treatment of acne and contraception, they should be evaluated regularly by a primary care provider for STI counseling and surveillance. Monitoring blood pressure for several months after starting COCs should also be done at follow-up visits as they may cause hypertension [123].

There is concern regarding COC use in pediatric populations regarding the effects of low estrogen and sufficient bone mass accrual. Peak bone mass occurs between the ages of 16–22 and some contend that building as much bone mass as possible prior to initiating exogenous estrogen therapy is crucial [31, 124]. Studies have not demonstrated osteopenia or an effect on bone mineral density with COC use [125, 126]. However, definitive conclusions are yet to be made. In general, use of COCs for acne should be avoided within two years of first starting menses, unless clinically indicated.

Isotretinoin

Oral isotretinoin is the most effective medication for severe acne as it is a disease-modifying agent that addresses all major aspects of acne pathogenesis. Initial isotretinoin studies were done on Caucasians; however, subsequent studies have demonstrated effectiveness in blacks as well [127]. Its indications and precautions are similar for all patients. Some experts recommend initiation of isotretinoin in skin of color with a lower initial dosing to avoid an inflammatory flare [46]. One review from Singapore with 82.3 % of Chinese patients described a starting dose of 0.4 mg/kg with a mean dose of 0.5 mg/kg for 7.8 months. Complete remission or significant improvement was found in 93.9 % of patients [128].

Proper counseling is essential in isotretinoin. Common and dose-related side effects include xerosis especially in the lips and eyes and myalgias. Emollient moisturizers can help relieve the drying effects. There is also the possibility of changes in serum triglycerides and liver enzymes. Screening laboratory data and subsequent monitoring are recommended.

Isotretinoin is a teratogen and can cause major fetal abnormalities with exposure. The FDA-mandated iPLEDGE program stipulates any female of childbearing potential must use two forms of highly effective contraception. It is imperative to have appropriate contraceptive counseling techniques. In addition to the multiple factors considered (e.g., maturity, finances, access to care and prescriptions, confidentiality, medical risks and benefits, and contraindications), there are racial and ethnic differences in teen pregnancies.

There are approximately 750,000 pregnancies annually among teenagers aged 15–19 in the United States with over 80 % of them unplanned [129]. There are large racial differences in unintended pregnancies [130]. About one-third of teenagers in high school (15–19 years of age) are sexually active and over 40 % have had sexual intercourse [131]. The prevalence of teenagers having sexual intercourse for the first time before age 13 years is 6.2 % [131]. There are also racial/ethnic differences in sexual debut. One study demonstrated the probability for a sexual debut by their 17th birthday was highest in African Americans (74 % females, 82 % males), followed by Hispanics (59 % females, 69 % males), then Caucasians (58 % females 53 % males), and finally, Asians (28 % females, 33 % males) [132]. Asian-American adolescents have been shown to have more sexually conservative attitudes and behaviors and may be more reluctant to start contraception [133]. Other barriers to effective contraception use may be practices in other countries. For example, in Iran, only 6.8 % of women used two forms of highly effective contraceptive methods during isotretinoin therapy [134].

User-dependent contraceptive methods (e.g., condoms, pills, patch, ring, injections) have a higher typical use failure rates [135, 136]. The pregnancy rate during typical use (inconsistent or incorrect use) for condoms is 18 % [136]. On average, adolescents miss up to three pills per cycle of COCs. Consequently, although the perfect use failure rate is about 0.3 %, the typical use failure rate is 9 %. The percentage is lower for depot medroxyprogesterone acetate (DMPA) (6 %) [135, 136]. Furthermore, a recent study demonstrated a twofold increase in contraceptive failure in women less than 21 years of age using the pill, patch, or ring, compared to older women. With long-acting reversible contracep-

tion (LARC) (e.g., intrauterine devices (IUD), implants), adolescents have a similar low failure rate as women 21 years of age and older [137]. LARC is user independent. After initial insertion, there is no maintenance, resulting in similar typical and perfect use failure rates [135]. For any teenager starting isotretinoin, with a known history of non-adherence with hormonal therapy or other prescriptive routines, these alternate forms of contraception should be strongly recommended.

Controversial adverse events associated with isotretinoin include bone effects, development of inflammatory bowel disease (IBD), and mood changes including depression, suicidal ideation, and suicide.

Bone homeostasis with isotretinoin exposure is complicated. In chronic, long-term use in keratinization diseases such as Darier's disease, ichthyosis, and palmar-plantar keratoderma, isotretinoin has been shown to influence bone mineral density [138–140]. Diffuse idiopathic skeletal hyperostosis (DISH) syndrome, ossification of ligaments particularly the spine, have also been reported with long-term isotretinoin use [141]. However, a recent study did not find any clinically radiographic abnormalities in acne patients who received long-term and/or multiple courses of isotretinoin [142]. There have been no studies that demonstrate clinically significant risk of bone changes due to short-term isotretinoin therapy.

The potential association between IBD and isotretinoin has become a popular topic in recent years [143]. It initially began with reports of isotretinoin causing an exacerbation of IBD [31, 144]. There have also been case reports and small case series ($n=18$) describing the occurrence of IBD after the initiation of isotretinoin. In a large case–control study using an US insurance claims database, researchers found only ulcerative colitis was associated with previous isotretinoin exposure. The risk of developing ulcerative colitis was associated with increase doses and duration of isotretinoin. The absolute risk was minimal [145]. However, a population-based case control study using data from a Canadian epidemiology database could not demonstrate an association between inflammatory bowel disease [146]. There are many confounding variables that make the association questionable including the presentation of IBD and acne at similar ages, the possibility of acne associated with IBD, and the history of antibiotic use and IBD [144, 147]. Despite the lack of definitive evidence on the causal relationship on isotretinoin, the FDA added IBD as possible adverse effect on isotretinoin's package insert.

Mood changes have also been associated with isotretinoin use, although causation has yet to be established. The majority of patients receiving isotretinoin for acne are in their adolescence which has been regarded as time of heightened emotional reactions and turbulence. Not surprising, there is a high prevalence of depression among adolescents. One cohort study demonstrated approximately a third of men and more than half of women had depressive and anxiety symptomatology at least once during adolescence [148]. In a review of all the reported psychiatric adverse events reported in 5 million patients on isotretinoin, 24 cases of depression, 4 suicides, and 3 attempted suicides from isotretinoin overdose were found [149]. Incidentally, more suicide attempts are made during the adolescent years than any other time in life. Among 9th–12th grade students in the United States, the prevalence of suicide attempts is about 7.8 % in comparison to 0.5 % among adults [150]. A systematic review of prospective and retrospective studies could not demonstrate an increase in depression or symptoms after isotretinoin treatment [151]. Subsequent studies evaluating this association could not find a relationship [152, 153]. In fact, two prospective studies found an improvement in quality of life and a reduction in depressive symptoms and suicidal ideation when the acne improved [154, 155]. However, given the severity and frequency of these problems among teenagers, it is vital to question patients on mood changes before and during isotretinoin therapy.

Adjunctive Therapies

There are other adjunctive therapies that can help improve the appearance of acne. Most of these methods are not suitable for monotherapy. Intralesional injection of triamcinolone acetonide (2.5–5 mg/cm^3) can help alleviate tenderness of inflammatory nodules [43]. Use can be limited in children due to the pain of injection. Comedone extraction after at least 4 weeks of retinoid therapy can help reduce future hyperpigmentation and improve the appearance in willing patients [56].

Chemical peels such as SA or low-strength glycolic acid can help address acne and PIH simultaneously. For darker skin types, superficial or medium depth peels are appropriate. In general, chemical peels are not appropriate for younger patients but may be used in select adolescents. Short application times (2–3 min) and low concentrations are key [43]. Patient selection is also very important as patients or parents with unrealistic expectations, history of excessive dyspigmentation/scarring, and lack of downtime would be reasons to defer treatment. A review of the effectiveness of chemical peels for acne noted the lack of quality of evidence with most studies being open label with no comparator, allowing concomitant use of other acne medications, and poorly stated end points [156]. It concluded there may be some advantages of chemical peels as an adjunctive treatment to prolong effects of medical treatment. Overall, chemical peels are safe. With its additional benefits of PIH reduction (see below), they may be a viable, adjunctive treatment option [157].

SA is a β-hydroxy acid that has lipophilic properties, which allow it to act mainly on the superficial layers of the

epidermis and sebaceous glands. This results in keratolysis by disrupting intercellular lipids. The comedolytic and anti-inflammatory properties make it effective for active acne and PIH. SA 20–30 % peels have been found to be safe in darker skin types [50, 157]. One study found biweekly 30 % SA peels to be effective in whitening and improvement of acne in Asian patients [158].

Glycolic acid is a α-hydroxy acid that induces epidermolysis, disperses melanin in the basal layer, and increases collagen synthesis [159]. The concentration ranges from 20 to 70 % and requires a neutralization process.

To prevent an irritant dermatitis and subsequent PIH, initiate treatment with lower concentration, titrating up as tolerated. Peels can be done every 2–4 weeks with discontinuation of retinoid 5–7 days prior to peel. The most common side effect of chemical peels is a transient PIH [50]. Hydroquinone can be used to reduce the PIH.

Light-based therapies such as blue light, diode laser, intense pulse light (IPL), and photodynamic therapy (PDT) have been reported to treat acne in skin of color. Again their use in children and younger adolescents may be limited by pain or length of procedure. The purposed mechanism of action of blue light therapy is the fluorescent porphyrins within *P. acnes* are targeted and destroyed by the blue light [160]. The 1,450 nm diode laser theoretically heats the sebaceous gland resulting in reduced sebum production. Its effectiveness with minimal side effects (transient PIH and erythema) was observed in two studies [161, 162]. IPL is thought to photoinactivate *P. acnes*, destroy sebaceous glands through photothermolysis, and have anti-inflammatory effects [163]. In 25 Japanese patients with moderate-to-severe acne, five sessions of IPL effectively reduced acne, but the majority of patients experienced transient PIH [163]. PDT works by using aminolevulinic acid to selectively induce porphyrin fluorescence of pilosebaceous units, thereby targeting *P. acnes* [164]. One case report describes clearance of moderate acne after using blue light PDT and 20 % aminolevulinic acid monthly for 4 months in an African-American with type V skin after failure with topical and oral antibiotics [165]. Two Asian studies have also described success with PDT in acne [166, 167]. Similar to topical and oral treatments, it is important to balance treatment with possible sequelae. Postinflammatory hyper- and hypopigmentation and even scarring can occur with these devices. Test spots and cooling devices are critical, although excessive cooling can cause PIH as well [168].

Sequelae

Treatment of the acne sequelae, postinflammatory changes and scarring, is a balancing act. It is prudent to emphasize, especially in pediatric patients, close observation for sequelae is important. Some key considerations include the patients' desire for treatment and understanding of the risks and discomforts. Aggressive therapies such as acne scar revision and laser therapies may be better suited for older adolescents. Many treatments for acne sequelae are invasive and cause cutaneous trauma which can worsen the appearance. Expectations need to be managed appropriately.

Prevention of sequelae is as important as treatment. Sun protection is imperative. In African-American communities, sun protective behaviors may need to be taught and emphasized, as there may be a lack of sun protection culture. Asians from Asia have traditionally been strict with their sun protection, associating fair skin with beauty [169]. However, Asian Americans have tended to embrace the Western ideals of beauty and may not practice sun protection [170]. Treating PIH and scarring is more difficult with sun exposure. Exposing hydroquinone to sunlight reverses its effects and causes repigmentation [171]. Exposure to sun before or after laser therapy can increase epidermal melanin pigmentation and epidermal thickness [168]. During therapy, physicians should be cautious of treatments that may cause pigmentation such as overaggressive topical retinoids or minocycline. Patients should also be warned against manipulation, such as squeezing or picking, as it may result in increased hyperpigmentation [172]. To avoid retinoid dermatitis choose a gentle formulation and the appropriate strength.

Dyspigmentation

Topical therapies to manage PIH include depigmenting agents, corticosteroids, and retinoids. Depigmenting agents include hydroquinone, 4-hydroxyanisole, azelaic acid, and kojic acid. Hydroquinone is the mainstay of treatment for bleaching. It suppresses tyrosinase, which inhibits melanogenesis and also releases semiquinones free radicals, which are toxic to melanosomes. Hydroquinone 2, 3, and 4 % are most commonly available with higher percentages available at compounding pharmacies [52]. Hydroquinone 2 and 3 % are available over the counter while 4 % requires a prescription. Hydroquinone 4 % is not FDA approved for children under the age of 12. The low concentrations of hydroquinone used in the United States are generally well tolerated. However, two cases of ochronosis-like reaction associated with hydroquinone 2 % use after several months have been reported [173, 174]. Bleaching creams in other countries tend to contain much higher concentrations of hydroquinone which can increase the risk of exogenous ochronosis [63, 175]. Therefore, when evaluating PIH, it is important to ask about what products are currently being used and when in doubt, ask patient to bring their products for review.

Azelaic acid (AA) 15–20 % and kojic acid are considered weaker agents compared to hydroquinone. Their mechanisms of action are comparable [48]. AA can also inhibit the energy production and subsequent DNA synthesis of

hyperactive melanocytes [176]. One study demonstrated improvement of PIH with AA 15 % gel used twice daily for 16 weeks [177]. Kojic acid may be appropriate for those who cannot tolerate hydroquinone [178].

Topical corticosteroids are thought to lighten the skin by reduction in melanin synthesis by inhibiting pro-opiomelanocortin (POMC) [179]. They are commonly used in Africa as skin lighteners and are available there without prescription [63]. In the United States, they are rarely used as monotherapy due to the risk of steroid atrophy and steroid-induced acne.

Retinoids have been shown to reduce PIH in skin of color. The exact mechanism by which retinoids reduce pigment is unknown; it likely inhibits the induction of melanogenesis [180]. In a study of 54 black subjects, tretinoin 0.1 % cream daily use resulted in a 40 % lightening effect when compared to 18 % with placebo. Half of the subjects treated with tretinoin did report moderate-to-severe erythema and desquamation [181]. Another 12-week study, comparing tretinoin microsphere 0.04 % gel to tazarotene cream 0.05 % in 40 patients (35 % black), demonstrated a reduction of more than 50 % dyspigmentation in both groups. However, in the tazarotene group, 5 % of the patients noted increased pigmentation [182]. Tazarotene 0.1 % cream (versus vehicle) in 74 patients with darker skin types with acne/PIH was also found to be effective and well tolerated [183].

A combination of products often achieves the best success. The addition of tretinoin and corticosteroid to hydroquinone is helpful as tretinoin can increase epidermal absorption of hydroquinone and prevent epidermal atrophy of corticosteroids [184]. The corticosteroid helps reduce the irritation of both hydroquinone and tretinoin. A case series of 20 Indian patients with skin types IV and V examined the use of hydroquinone 2 %, tretinoin 0.05 %, and fluocinolone acetonide 0.01 % cream nightly with serial glycolic acid peels for PIH and found improvement [185].

Dermal hyperpigmentation is more difficult to treat. One study examined the histologic features of 10 biopsies obtained from Japanese patients using tretinoin gel (0.1 %, 0.2 %, and 0.4 %) with 5 % hydroquinone and determined the combination was not effective in reducing dermal melanosis [186].

Scarring

Intralesional triamcinolone acetonide is typically used to treat keloids or hypertrophic scars. Higher concentrations (20–40 mg/cm^3) are needed and repeated at 4-week intervals [43]. Adverse effects include hypopigmentation and atrophy. Surgical removal of keloids can also be done with serial corticosteroid injections to reduce chance of recurrence. For atrophic scarring, depending on the type of scar, filler agents, chemical peels, microdermabrasion, and surgical therapy can be done. Keratolytics such as tricholoroacetic acid (TCA) result in the swelling and softening of the epidermis with subsequent desquamation [52]. It is especially useful for atrophic scars. Its use may be limited in darker skin types as it can cause epidermal necrosis and permanent depigmentation or scarring [187]. Surgical techniques include elliptical excision, punch excision, punch elevation, subcision (subcutaneous incision), dermal grafting, dermabrasion, and laser skin resurfacing [188].

Laser therapies have also been used to reduce PIH and scarring with variable success. Vascular lasers such as the 595 nm long-pulsed dye laser (L-PDL) have been used to reduce acne-induced PIH [189]. It is thought to be effective by treating the vascular component of inflammation thereby reducing inflammation and risk of PIH. At low fluence settings, the 1,064 nm Q-switched Nd:yittrium aluminum garnet (QS Nd:YAG) laser has also been used to treat PIH. Kim and Cho compared two groups of Korean patients with PIH and mild-to-moderate acne with one group ($n=20$) treated with 5 weekly treatments of full face low fluence 1064 nm QS Nd:YAG laser treatment with comedone extraction and intralesional injections for severe inflammatory papules and topical 4 % BP gel twice daily and the other group ($n=20$) with comedone extraction and intralesional injections for severe inflammatory papules and topical 4 % BP gel twice daily. They found a reduction in PIH in the QS:Nd YAG group [190]. Side effects of low fluence 1,064 nm QS Nd: YAG include confetti-like hypopigmented macules and rebound hyperpigmentation [168]. Nonablative fractional resurfacing [191] and ablative fractional resurfacing have both been studied for treatment of PIH and scarring. In theory, fractional photothermolysis should be safe and effective in darker skin types because it produces microscopic columns of thermal injury. However, results for both ablative and nonablative lasers are inconsistent and the risk for PIH is high [45].

Prognosis

Prognosis for acne itself is good. Even without treatment, acne tends to resolve with time. However, especially in skin of color, the sequelae of acne, without proper education and treatment, can remain and continue to be a source of anxiety. Early treatment is crucial to prevent PIH and scarring.

Ongoing Research

There is ongoing research examining acne in pediatric populations and in skin of color. Most recently, adapalene 0.1 % gel/BP 5 % fixed-combination gel (Epiduo®) was studied in the 9–11-year-old population and there are ongoing studies on other commonly used acne products on the 9–11 years of age population (NCT00907335). Additionally, there is

a prospective study on the effects of isotretinoin on the musculoskeletal system in a pediatric population (NCT00964119). There are several ongoing studies on diet and acne. PIH and effective treatments are areas with promising new developments especially with laser procedures. Large studies on darker skin types need to be done to determine safe treatment parameters.

Conclusion

As demographics continue to evolve, it will become increasingly difficult to classify patients based on ethnicity and how their skin will respond to acne. Therefore, it is important to evaluate each patient as an individual and determine treatment based on medical history and clinical examination. When treating those with acne who have prominent PIH and scarring, treating their acne is only half of the management regimen. The second part is effective treatment of the sequelae. Addressing both components is essential to achieving the delicate balance between excellent acne control and sustained patient satisfaction.

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Periorificial Dermatitis

39

Adena E. Rosenblatt and Sarah L. Stein

Abstract

Periorificial dermatitis is an eruption of papules and sometimes pustules of unclear etiology. In the pediatric population, it is commonly seen in prepubescent patients. The typical morphology is of monomorphous grouped papules in a perioral, perinasal, or periocular distribution. These lesions range from pink to red to flesh colored and may be associated with hypo- or hyperpigmentation, particularly in dark-skinned patients. There is usually a clear zone between the vermilion border of the lip and the affected area. Childhood granulomatous periorificial dermatitis is a subtype of periorificial dermatitis that is characterized by yellow-brown or erythematous papules without pustules; the pathology demonstrates perifollicular non-caseating epithelioid granulomas. This subtype, also known as facial Afro-Caribbean childhood eruption (FACE), is more common in skin of color.

Topical, inhaled, or systemic corticosteroid use is frequently associated with periorificial dermatitis. It is important to ask about use of bleaching creams since many of these products contain corticosteroids. Topical metronidazole and oral erythromycin are the mainstays of treatment for this condition in children.

Keywords

Periorificial dermatitis • Perioral dermatitis • Facial Afro-Caribbean childhood eruption • Childhood granulomatous periorificial dermatitis

Abbreviations

CGPD Childhood granulomatous periorificial dermatitis
FACE Facial Afro-Caribbean childhood eruption

Introduction

Periorificial dermatitis is an eruption of papules and pustules of unclear etiology. It occurs most commonly around the mouth, but can also occur around the eyes, nose, and rarely in the groin. The first description of periorificial dermatitis was in 1957 by Frumess and Lewis who described a cyclic dermatitis affecting the skin of the perioral region principally among young females, which they titled light-sensitive seborrheid [1]. This eruption is now termed perioral or more specifically periorificial dermatitis since it can occur in not only a perioral but also perinasal and periocular distribution. This is a cutaneous condition without significant systemic manifestations.

A variant of periorificial dermatitis is childhood granulomatous periorificial dermatitis (CGPD) also known as facial Afro-Caribbean childhood eruption (FACE). This variant is more commonly seen in patients with skin of color. CGPD was first described in 1970 by Gianotti who reported a series of five Italian children with monomorphous papules around the mouth with a granulomatous pattern on histology. The term FACE was coined by Williams in 1990 with his report of five African-American children with CGPD [2].

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Epidemiology

- **Occurs equally in boys and girls.**
- **History of recent inhaled or topical corticosteroid use is common.**
- **Granulomatous variant is usually seen in dark-skinned individuals**

Periorificial dermatitis is more common in adults than children [3]. When it is seen in children they are typically prepubescent [3]. However, the age range of periorificial dermatitis in children has been reported from 6 months to 18 years. There are only a few studies examining the demographics of periorificial dermatitis in children. Most studies show an equal prevalence in girls and boys; however some reports suggest a slight female predominance of about 58 % compared to 42 % in boys [4, 5]. Periorificial dermatitis is seen in both Caucasian patients and patients with skin of color.

CGPD is described more commonly in dark-skinned individuals. There is debate in the literature over whether there is truly a predominance of this condition in patients with skin of color or simply a bias reflecting the demographics of the patients in the reported cases. There are a variety of ethnicities in which CGPD has been identified (Table 39.1), including Korean, Japanese, Hispanic, Jamaican, African-American, Brazilian, Bolivian, German, Italian, Madagascan, Hispanic American, and Caucasian American children [2, 3, 6–18].

Table 39.1 Reports of childhood granulomatous periorificial dermatitis by ethnic and racial groups

Ethnic or racial group	Number of patients reported
Korean	5
Japanese	2
Brazilian	1
Bolivian	1
Madagascan	1
Italian	5
German	11
Caucasian American	6
Hispanic American	2
African American	28
Jamaican	1

There are many etiologic factors implicated in periorificial dermatitis and CGPD (Table 39.2). The most common is systemic, topical, or inhaled corticosteroid use [4, 6]. About half of the patients with periorificial dermatitis present with a history of recent corticosteroid use [19]. The fluorinated corticosteroids appear to be the most problematic. Interestingly, in some patients, topical, inhaled, and systemic corticosteroids can temporarily improve periorificial dermatitis. However, a rebound effect is commonly observed after discontinuation of the corticosteroid medication [4]. A particular consideration in dark-skinned patients is the possible contribution of over-the-counter bleaching agents. These products are frequently used by patients with skin of color and may contain corticosteroids that could exacerbate periorificial dermatitis. Many of the bleaching agents that are available over the counter outside of the United States are known to contain potent corticosteroids, and these products may be imported by patients, their families, or even sold in ethnic stores within the United States.

Other factors which have been associated with the development of periorificial dermatitis include fluorinated toothpastes and overuse of skin-care ointments and creams, especially those with petrolatum or paraffin base or an isopropyl myristate vehicle [1, 20]. One of the proposed mechanisms is that persistent hydration of the horny layer from overuse of moisturizers may lead to impaired barrier function and proliferation of skin flora, resulting in the papular eruption. Physical sunscreens with high sun protection factors have also been implicated in periorificial dermatitis, particularly in patients with atopic dermatitis and poor skin barrier function [21]. In addition, physical factors such as ultraviolet light exposure, heat, such as from use of hot water, and wind have been associated with development of periorificial dermatitis [1].

There are also infectious agents including fusiform spirilla bacteria, *Candida* species, and *Demodex folliculorum* that have been implicated in the pathogenesis of this condition. *Fusobacterium* overgrowth is often found after use of fluorinated topical corticosteroids [1]. There is one reported case of CGPD that occurred after varicella vaccination [7]. A variety of other factors have also been associated with periorificial dermatitis including use of oral contraceptives, conditions of GI malabsorption, emotional stress, musical instruments, latex gloves, lipstick, essential oils in bubble gum, greases, formaldehyde preservatives, antiseptic solutions, black synthetic mesh, drooling, and lip-licking cheilitis [1, 7]. Finally, there appears to be an increased risk of periorificial dermatitis in immunocompromised children, especially in those patients with leukemia [1].

Clinical Presentation

- **Usually a perioral distribution, but perinasal and periocular are also seen**
- **Mostly monomorphous small grouped papules with erythema and variable scale**
- **Rarely symptomatic**

Periorificial dermatitis usually presents as grouped very small erythematous to pink papules, occasionally with vesicles and pustules, sometimes with surrounding erythema and fine scale (Fig. 39.1) [4]. Papules can appear more flesh colored in darker skinned individuals. Furthermore, hyperpigmentation

Table 39.2 Etiologic factors associated with periorificial dermatitis

Etiologic factors	
Corticosteroids	Inhaled
	Topical (particularly fluorinated)
	Systemic
Cosmetics and skin care products	Moisturizers (petroleum or paraffin base)
	Bleaching creams
	Essential oils
	Lipstick
	Greases
	Physical sunscreens with high SPF
	Antiseptic solutions
Medications/vaccines	Oral contraceptives
	Fluorinated toothpaste
	Varicella vaccine
Microorganisms	*Candida* species
	Fusiform spirilla bacteria
	Demodex folliculorum
	Fusobacterium
Physical factors	Ultraviolet light
	Heat
	Wind
	Hot water
	Drooling
Preexisting medical conditions	GI malabsorption
	Lip-licking cheilitis
	Immunosuppression (esp. leukemia)
	Emotional stress
Other	Latex gloves
	Black synthetic mesh
	Musical instruments
	Bubble gum
	Formaldehyde

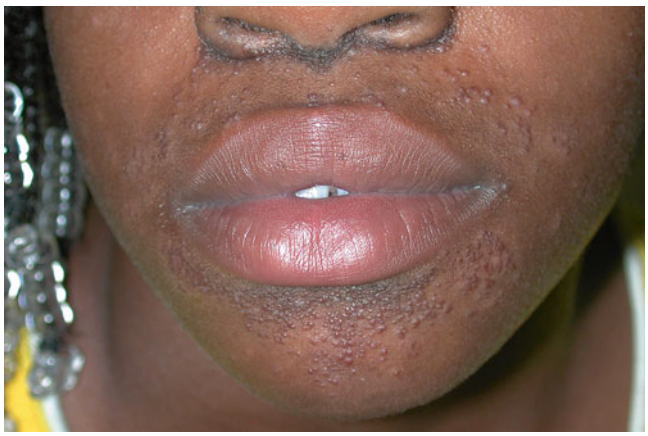

Fig. 39.1 An African-American girl with multiple erythematous monomorphic papules in a perioral distribution

and hypopigmentation can be seen in patients with skin of color (Fig. 39.2). Papules, vesicles, and pustules are usually ~1–3 mm in size and in the same stage. The lesions are in a

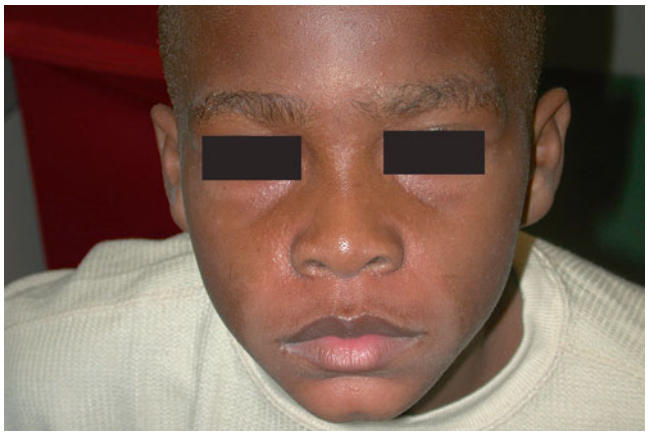

Fig. 39.2 An African-American boy with multiple flesh-colored papules with surrounding hypopigmentation in a perioral distribution

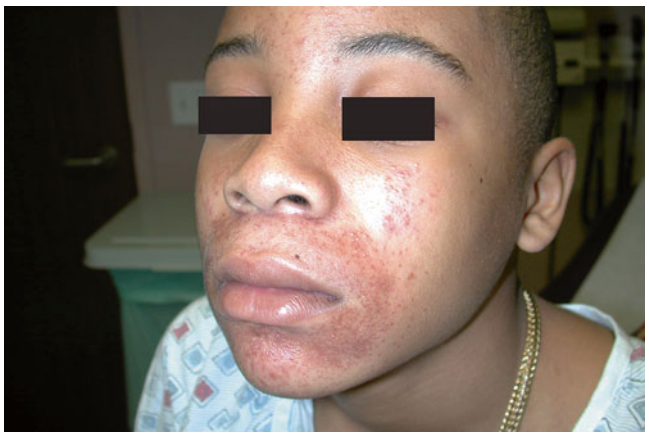

Fig. 39.3 An African-American boy with erythematous monomorphous grouped papules in a perioral, perinasal, and periocular distribution

perioral distribution in 70–100 % of cases, perinasal in 43–57 %, and periocular in about 25 % (Fig. 39.3). Papules and pustules less commonly appear on the cheeks, chin, neck, and forehead. Lesions may recur over weeks to months [1]. There is usually a 3–5 mm border of normal skin separating the vermilion border of the lips from the affected area (Fig. 39.4) [1]. This can be a helpful clue in determining the diagnosis. In majority of the cases the eruption is asymptomatic, but a subset of patients experience pruritus and sometimes a burning sensation. The differential diagnosis may include acne vulgaris, seborrheic dermatitis, impetigo, acrodermatitis enteropathica, and tinea faciei.

Patients with CGPD usually present with monomorphous dome-shaped discrete yellow-brown or erythematous papules in a perioral, perinasal, or periocular distribution. Unlike periorificial dermatitis, pustules are rarely seen. There is also less erythema and scaling in CGPD compared to periorificial dermatitis (Fig. 39.5) [7]. Occasionally, patients

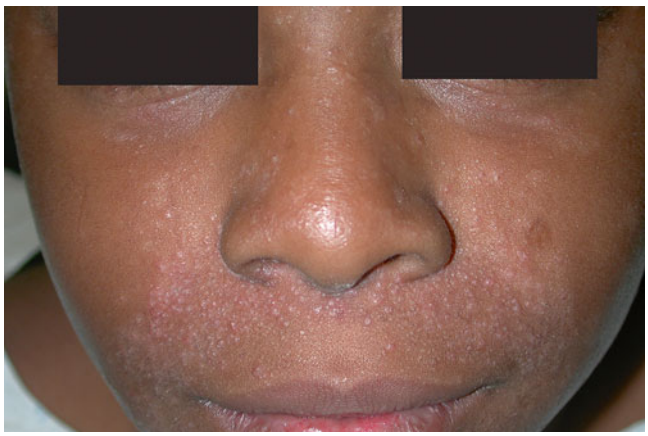

Fig. 39.4 Area of clearing between the vermilion border and the affected area

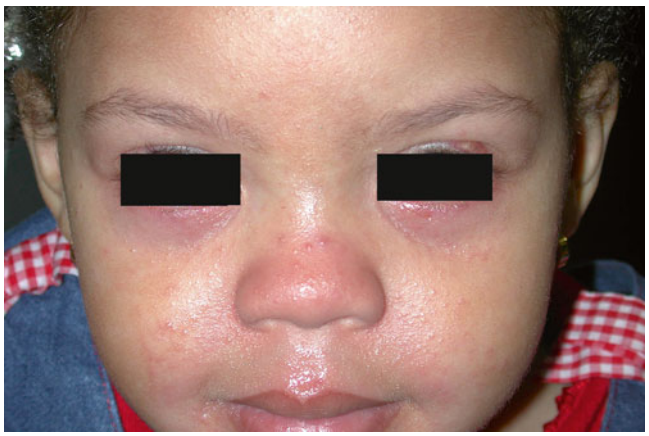

Fig. 39.6 An African-American girl with perioral dermatitis and a chalazion

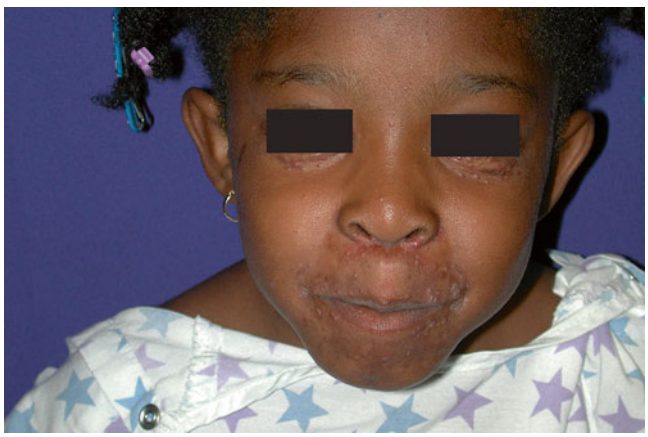

Fig. 39.5 An African-American girl with erythematous monomorphous papules in a perioral and periocular distribution

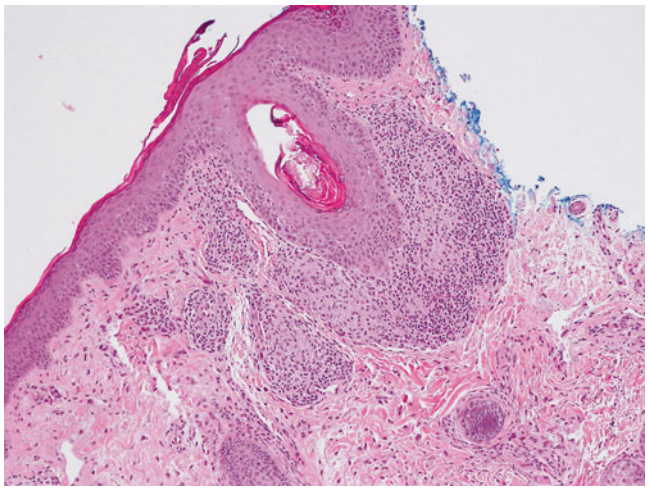

Fig. 39.7 Histology CGPD with perifollicular discrete non-caseating epithelioid granulomas

have blepharitis, conjunctivitis, or chalazion (Fig. 39.6) [7]. Cases of generalized lesions on the extremities, trunk, and labia majora have also been reported [7]. In addition to the differential diagnosis already, discussed the differential for CBGD also include sarcoidosis, granulomatous-type infections, and lupus miliaris disseminata faciei.

Diagnosis of periorificial dermatitis and CGPD is usually based on the patient's history and clinical features. The dermatopathology differs somewhat between periorificial dermatitis and CGPD. The histopathology of periorificial dermatitis is similar to rosacea. A biopsy from the chin or nasolabial groove that includes at least one papule is recommended. Early lesions are characterized by parakeratosis, mild acanthosis, spongiosis, and ectatic venules. A perifollicular lymphocytic infiltrate is typical. Later lesions can have diffuse hypertrophy of connective tissue and hyperplasia of sebaceous follicles in addition to a perifollicular and perivascular lymphohistiocytic infiltrate. Lesions of CBGD demonstrate perifollicular discrete non-caseating epithelioid granulomas, with a few Langerhans cells in the dermis (Fig. 39.7). Mild moderate spongiosis may also be present.

Treatment

- **Topical metronidazole is a frequent treatment in children**
- **Oral antibiotics with anti-inflammatory activity, particularly erythromycin, are effective for children not responding to topical treatment**
- **Discontinue topical, systemic, or inhaled steroids if possible**

Oral erythromycin and topical metronidazole twice a day are the mainstay treatments for periorificial dermatitis and CGPD in children [3, 4, 22]. The effective treatment course for oral erythromycin is 30–50 mg/kg/day divided every 6–12 h for 4–6 weeks. The average time of clearance of lesions with topical metronidazole is 7 weeks, but a range of 1 week to 6 months has been reported in the literature [4, 19, 23].

Oral tetracyclines (tetracycline, doxycycline, minocycline) are a common treatment for periorificial dermatitis in adults and have been found to be more effective than topical metronidazole in this population [24]. Doxycycline and minocycline are usually prescribed at doses of 100 mg PO 1–2 times a day. However, tetracyclines are not recommended in children under 8 years old due to the risk of permanent teeth discoloration [1]. In addition to the use of oral tetracyclines and macrolides, there are reports of effective treatment with oral metronidazole as well as beta lactam antibiotics [16]. Cefcapene pivoxil hydrochloride hydrate, a beta lactam antibiotic, at 100–300 mg/day was used in three patients with *Fusobacterium*-associated periorificial dermatitis with significant improvement of the dermatitis as well as clearance of the *Fusobacterium* [17].

Treatment with topical agents including calcineurin inhibitors, azelaic acid, clindamycin, erythromycin, and sodium sulfacetamide may be effective as a second-line approach [1, 18, 25, 26]. Isotretinoin has also been reported to be effective in the treatment of periorificial dermatitis [27]. There is one report of the use of ALA-PDT in the treatment of periorificial dermatitis [28]. There are conflicting reports regarding the use of benzoyl peroxide and adapalene in periorificial dermatitis. Some studies found it to be an effective adjuvant treatment, while others report that these topical medications can exacerbate the condition given the risk of skin irritation with these products [1].

It is important that all corticosteroids be discontinued if possible. Patients should be counseled of the risk of a flare-up when the corticosteroids are stopped, and hydrocortisone 1 % cream can be used to wean patients who have been on chronic topical, inhaled, or systemic corticosteroids, in order to reduce the risk of a rebound after sudden discontinuation of more potent corticosteroids [26].

Prognosis

The prognosis for periorificial dermatitis and CGPD is excellent. Treatment can clear the condition within 2–3 months. However, too brief treatment courses may result in recurrent episodes. Spontaneous resolution of periorificial dermatitis may occur within months to 3 years after onset of the eruption [7]. It is important to remember that sudden discontinuation of topical, systemic, or inhaled corticosteroids can result in a flare-up of the condition.

Ongoing Research

Ongoing research on periorificial dermatitis in children is limited. The majority of the publications are case reports and retrospective studies evaluating possible etiologic factors or treatment options. The precise pathophysiology of this condition has not been elucidated.

Conclusion

Periorificial dermatitis of all types is commonly seen in prepubescent patients. The typical morphology is of monomorphous grouped papules in a perioral, perinasal, or periocular distribution. These lesions range from pink to red to flesh colored and may be associated with hypo- or hyperpigmentation, particularly in dark-skinned patients. There is usually a clear zone between the vermilion border of the lip and the affected area. CGPD is a subtype of periorificial dermatitis that is characterized by yellow-brown or erythematous papules without pustules; the pathology demonstrates perifollicular non-caseating epithelioid granulomas.

Topical, inhaled, or systemic corticosteroid use is frequently associated with periorificial dermatitis. It is important to ask about use of bleaching creams since many of these products contain corticosteroids. Topical metronidazole and oral erythromycin are the mainstays of treatment of this condition in children.

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Part VIII

Photosensitivity

Photosensitivity and Photoreactions in Pediatric Skin of Color

40

Meghan A. Feely and Vincent A. De Leo

Abstract

Photosensitivity is associated with a number of conditions in pediatric patients. These disorders can be organized into six categories that include (1) collagen vascular diseases, (2) idiopathic photodermatoses, (3) genetic and metabolic disorders, (4) nutritional deficiencies, (5) exogenous causes, and (6) photoaggravated conditions. An overview of the wide breadth of disorders in these subclasses is provided, with the focus of the discussion dedicated to photosensitivities, namely lupus erythematosus, actinic prurigo, hydroa vacciniforme, polymorphous light eruption, Hermansky–Pudlak syndrome, and specific subtypes of oculocutaneous albinism, with the strongest association in children of color. The epidemiologic and demographic data, clinical characteristics of these conditions, therapeutic options, prognosis, and areas of future research are reviewed. A sound understanding of these various facets will enable early diagnosis and treatment, thereby abating potential long-term sequelae of ultraviolet light exposure in children of color with photosensitizing disorders.

Keywords

Photosensitivity • Photoreactions • Lupus erythematosus • Actinic prurigo • Hydroa vacciniforme • Polymorphous light eruption • Hermansky–Pudlak syndrome • Oculocutaneous albinism

Background/Introduction

Photosensitivity is excessive sensitivity to light and is the cause of and may be associated with a number of dermatologic disorders in pediatric patients. It should be suspected in a child who develops a rash in a photodistributed distribution (i.e., the prominences of the midface and the extensor forearms) or when eruptions develop after sun exposure. These conditions can be organized into six subclasses, which include (1) collagen vascular diseases, (2) idiopathic photodermatoses, (3) genetic and metabolic disorders, (4) nutritional deficiencies, (5) exogenous causes, and (6) photoaggravated conditions (Table 40.1).

This chapter provides an overview of these disorders, with a focus on photosensitivities with the strongest association to children of color. These include lupus erythematosus (both systemic and cutaneous), actinic prurigo, hydroa vacciniforme, polymorphous light eruption (PMLE), Hermansky–Pudlak syndrome (HPS), and some subtypes of oculocutaneous albinism. The epidemiology and demographics, clinical findings, therapeutic options, prognosis, and areas of future research are discussed.

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Table 40.1 Photosensitivity and photoreactions in pediatric patients

Collagen vascular diseases	Neonatal lupus erythematosus Childhood systemic lupus erythematosus Childhood discoid lupus erythematosus Juvenile dermatomyositis
Idiopathic photodermatoses	Actinic prurigo Hydroa vacciniforme Polymorphous light eruption Solar urticaria
Genetic and metabolic conditions	Hermansky–Pudlak syndrome Bloom syndrome Rothmund–Thomson syndrome Kindler syndrome Trichothiodystrophy Cockayne syndrome Xeroderma pigmentosum Ultraviolet sensitive syndrome Albinism Hartnup disease Smith–Lemli–Opitz syndrome Phenylketonuria Hepatic porphyrias – Porphyria cutanea tarda – Variegate porphyria – Hereditary coproporphyria – Hepatoerythrocytic porphyria Erythropoietic porphyrias – Congenital erythropoietic porphyria – Erythropoietic protoporphyria
Nutritional deficiencies	Pellagra
Exogenous causes	Drug-induced photosensitivity Phytophotodermatitis
Photoaggravated conditions	Atopic dermatitis Psoriasis Seborrheic dermatitis Darier's disease Herpes simplex Acne vulgaris Rosacea Pityriasis rubra pilaris Dermatitis herpetiformis

Collagen Vascular Diseases

The collagen vascular diseases associated with photosensitivity in childhood include neonatal lupus erythematosus (NLE), childhood systemic lupus erythematosus (SLE), childhood discoid lupus erythematosus (DLE), and juvenile dermatomyositis (JDMS) [1–3]. Here NLE, SLE and DLE are discussed in further detail, given their increased prevalence in children of color.

While JDMS is not fully reviewed in this chapter because it is not necessarily more common in children of color, two facts pertaining to that disorder in patients who are African-American and Hispanic will be noted. First, patients of color with dermatomyositis have linkage to the HLA-DQA1 allele DQA1*0501 [4] and second, the clinical presentation of the skin lesions and heliotrope rash show more hyperpigmentation than violaceous lesions [5].

Neonatal Lupus Erythematosus

Epidemiology/Demographics

- Reported in African-Americans, Caucasians, Hispanics and Asians in the United States, and in numerous ethnicities internationally.
- No consensus regarding male or female predominance, although a study from the United States National Lupus Registry demonstrates an equal sex distribution.
- Incidence of 1:20,000 births, with greater associated morbidity and mortality in children of color.

Ethnic and Racial Groups Affected [6–13]
African-American, Caucasian, Hispanic, Asian

NLE is caused by transplacental transfer of maternal anti-SSA/Ro-SSB/La IgG antibodies, although in rare cases anti-U1 RNP antibodies have been implicated [14]. Mothers generally have Sjogren syndrome, SLE, rheumatoid arthritis, or other connective tissue disorders, although in the majority of cases the mother is unaware of her disease [2]. The affected neonate may present with cutaneous, cardiac, hepatobiliary, or hematologic abnormalities. In a prospective study of 128 neonates with neonatal lupus, there was a 16 % incidence of skin involvement [15], while other studies note cutaneous findings in half to three-quarters of patients [2, 16, 17].

In the multiethnic/racial Research Registry for Neonatal Lupus (RRNL), the demographics of mothers of 297 children with anti-SSA/Ro-related cardiac NLE were as follows: Caucasian (75.1 %), Black (9.1 %), Hispanic (8.8 %), Asian (4.7 %), and mixed race (2.4 %). Demographics for the RRNL as a whole are not provided in the publication [6]. There are reports from the United States [7], China [8], and Japan that assert female infant predominance [9], whereas others have demonstrated male infant predominance [10]. An incidence of 1:20,000 births has been reported [11]. Non-Caucasian neonates have a greater risk of associated morbidity and mortality [12].

Clinical Presentation

- Neonatal lupus is associated with cutaneous, cardiac, hematologic, and hepatobiliary abnormalities.
- Cutaneous findings have been variably reported to occur in 16–75 % of patients in different series.
- Skin findings characterized as erythematous, arcuate, or annular plaques with elevated active margins and mild central atrophy, often on the scalp or periorbitally although other areas can be involved.
- The sequelae of NLE can be long-term hyperpigmentation or hypopigmentation [13].

Clinically, NLE is associated with cutaneous findings, similar to subacute cutaneous lupus, cardiomyopathy, congenital heart block (CHB), hematologic irregularities, and hepatobiliary disorders [18, 19]. Erythematous arcuate or annular plaques (Fig. 40.1) with elevated active margins and

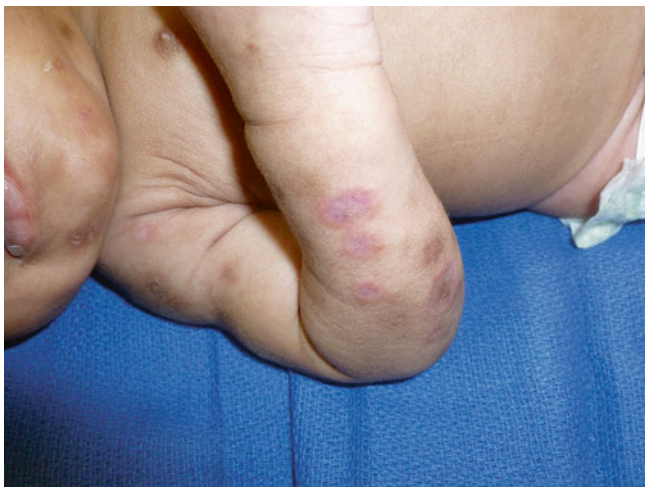

Fig. 40.1 Classical subacute cutaneous lupus like plaques in NLE (photo courtesy of Nanette Silverberg, MD)

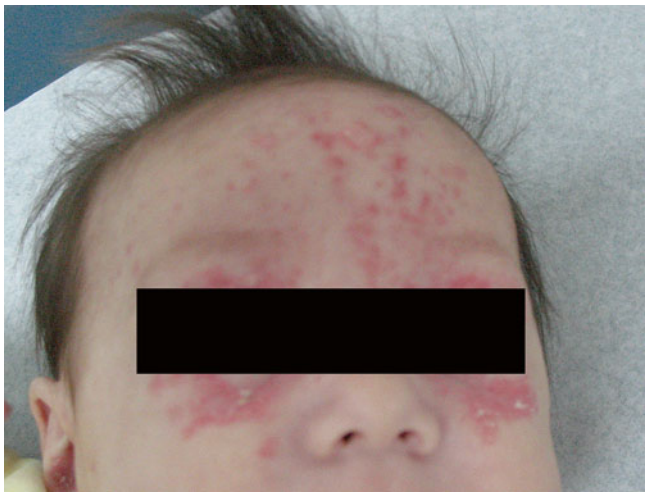

Fig. 40.2 Raccoon eyes with periocular telangiectases in NLE (photo courtesy of Nanette Silverberg, MD). From Springer from Atlas of Cutaneous Biodiversity, Fig. 9.3

mild central atrophy generally present periorbitally and on the scalp although other areas of the body can be involved. As stated earlier there are variable reports of skin manifestations in 16 to 75 % of NLE patients [2, 16, 17]. Other cutaneous findings may include congenital erosive lesions, periocular lesions termed raccoon eyes (Fig. 40.2), and, in lighter skinned children, telangiectases can be noted.

Cardiac screening is important in all children with NLE, however, the incidence of cardiac lesions in children who present with cutaneous lesions is not high when neonatal heart block is not detected. As there may be an undetected first-degree heart block that could evolve in the postnatal period, an electrocardiogram and at times an echocardiogram are performed, in addition to appropriate rheumatologic (ANA, SS-A, SS-B, and U1RNP antibodies), hematologic, and hepatic screening [7, 20].

Table 40.2 Treatments for neonatal lupus erythematosus [7, 16, 20–24]

Photoprotection	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance
Dermatologic therapies	Topical regimens such as low-potency corticosteroids or calcineurin inhibitors may be tried but do not lead to superior outcomes
Other subspecialties	Given the risk of congenital heart block, cardiomyopathy, hematologic and hepatobiliary disorders, involvement of other pediatric subspecialties and screening for these complications with appropriate therapies are indicated

Treatment, Prognosis, and Ongoing Research

- Photoprotection with broad-spectrum sunscreen, photoprotective clothing, and sun avoidance.
- Low-potency corticosteroids or calcineurin inhibitors may be tried, but it is unknown whether they lead to superior outcomes.
- Coordination of care with other pediatric, including cardiology, hematology, and gastroenterology, where needed.

The mean age of presentation and mean duration of skin lesions according to a National Registry in the United States were respectively 6 and 17 weeks. In that study there were no significant sequelae in 65 % of children while 25 % had resultant postinflammatory dyspigmentation and telangiectasias and a few children developed autoimmune disorders, such as juvenile rheumatoid arthritis and Hashimoto's thyroiditis. This elevated risk of autoimmune disease has been demonstrated in other studies, although there does not appear to be a higher risk of developing SLE. Photoprotection and topical regimens such as low-potency corticosteroids or calcineurin inhibitors may be tried but it is not known if they lead to superior long-term cosmetic outcomes [16, 21] (Table 40.2).

CHB can be detected during the pregnancy, and monitoring with Doppler echocardiograms or other modalities is recommended in women with anti-SSA/Ro-SSB/La antibodies to ensure that arrhythmia is identified and treated. The 3-month mortality rate in children with complete CHB has been reported as 15 % [22, 25]. Treatment for cardiac complications of neonatal lupus involves a pediatric cardiologist with close echocardiographic monitoring and often glucocorticosteroids for neonates with incomplete heart block, hydrops fetalis, ascites, or pleural effusions [20]. Early introduction of hydroxychloroquine is recommended in pregnancies with anti-SSA/Ro antibodies if there was a prior childbirth associated with cardiac manifestations of neonatal lupus. These medications, however, do carry risks during pregnancy [11, 23, 26]. Despite cardiac pacing and other interventions, dilated cardiomyopathy can develop in children with CHB, which may lead to congestive heart failure or a need for cardiac transplant [24]. A better understanding of the pathogenesis of NLE is necessary for developing therapeutics for this serious disorder.

Experimental

The role of L-type calcium channels in the cardiac manifestation of NLE in animal models may afford gene-targeted therapies [23].

Childhood Systemic Lupus Erythematosus

Epidemiology/Demographics

- Higher incidence in African-American, Hispanic, and Asian children with a lower reported incidence in Caucasians and Native Americans.
- 1:1 prepubertal female:male ratio with a 4.5:1 female predominance after puberty.
- Incidence of 1:10,000 with 15–20 % of SLE cases presenting by age 20 with the following age distribution: 11–15 years (60 %), 5–10 years (35 %), and <5 (5 %).

Ethnic and Racial Groups Affected [27]
African-American, Caucasian, Asian, Native American

SLE is a condition that can present with cutaneous manifestations such as a malar rash, photosensitivity, or discoid lesions [28, 29]. In 15–20 % of patients, the disease presents by age 20. In that subset, the age range for 60 % of those patients is 11–15 years, 35 % from 5 to 10 years, and 5 % in those less than 5 years [2]. The female:male ratio has been reported as 1:1 in prepubertal children with a 4.5:1 female predominance after puberty [2, 30]. In a study examining over 30 million children with Medicaid from 2000 to 2004, the prevalence was approximately 1:10,000 84 % of whom were females, with the following demographic data: African-American (40.9 % of total cases, incidence 2.73), Hispanic (23.7 %, incidence 2.45), Caucasian (22.1 %, incidence 1.33), Asian (6.1 %, incidence 4.16), and Native American (0.9 %, incidence 1.61) [27]. There is a higher risk of nephritis in children as opposed to adults with the highest incidence in non-Caucasian children. African-American children are often younger at diagnosis [31].

Clinical Presentation

- Diagnosis is based on meeting 4 of 11 criteria in the guidelines of the American College of Rheumatology, which includes three cutaneous features—a malar rash, a discoid rash, and photosensitivity.
- The malar rash of SLE presents as thin erythematous plaques with scale on the bilateral cheeks, sparing the nasolabial folds.
- The presence of discoid lesions on more than one body segment has an association with systemic disease and there is a higher association and progression of systemic involvement in children with DLE than in their adult counterparts.

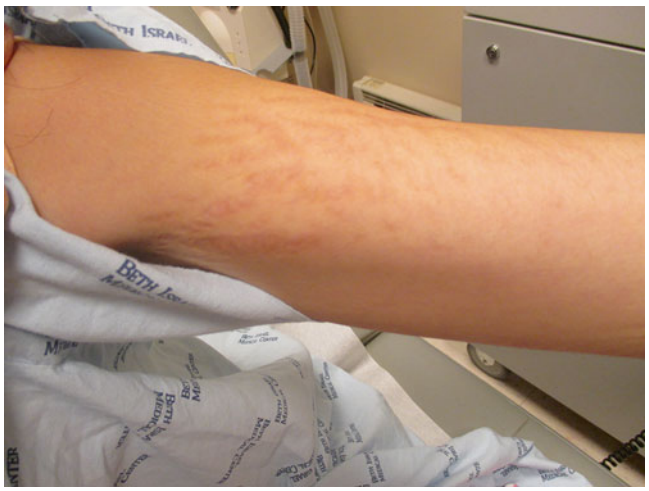

Fig. 40.3 Striae in an otherwise thin Hispanic girl receiving high dose oral steroid medication (photo courtesy of Nanette Silverberg, MD)

The diagnosis of SLE is based on the American College of Rheumatology guidelines, for which 4 of 11 criteria must be met. These criteria include malar or discoid rash, photosensitivity, mucocutaneous ulcerations, serositis, arthritis, immunologic, hematologic, renal or neurologic disorders, or elevated antinuclear antibody (ANA). Constitutional symptoms such as fatigue, myalgias, and fevers may be presenting symptoms [28, 29]. The malar rash of SLE presents as thin erythematous plaques with scale on bilateral cheeks sparing the nasolabial folds (Fig. 40.3). On the dorsal hands, there are periungual telangiectasias and sparing of the knuckles as opposed to JDMS where hyperpigmented lichenoid to flat plaques can be noted over the joints (corresponding to violaceous lichenoid papules seen in Caucasian patients). Discoid lesions may also be present. The presence of discoid lesions on greater than a single body segment in children is strongly associated with systemic disease. Often discoid lesions are an early cutaneous manifestation of SLE and there is a higher association with systemic involvement in children than in adults with discoid lupus [2]. Children with DLE should be tested for SLE and observed closely over time when the latter cannot be diagnosed.

Treatment, Prognosis, and Ongoing Research

- Use of NSAIDs for arthritis and other musculoskeletal involvement.
- Systemic glucocorticosteroids in conjunction with steroid-sparing disease-modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine for skin and systemic involvement.
- Use of agents like methotrexate for arthritis and azathioprine and cyclophosphamide for lupus-associated nephri-

Table 40.3 Treatments for childhood systemic lupus erythematosus [28, 29, 33–35]

Drug	Indication
NSAIDs (i.e. ibuprofen)	Arthritis and myalgias
Prednisone	Skin disease, serositis, arthritis or acute moderate-severe disease
Methylprednisolone	Acute severe renal, neurologic or hematologic disease
Hydroxychloroquine	Prevention of flares and constitutional symptoms, arthritis, skin involvement, improves lipids
Methotrexate	Arthritis, monitor kidney function due to renal metabolism
Azathioprine	Renal, neurologic, hematologic or vasculitic involvement
Cyclophosphamide	Best recorded success in severe neurologic or renal disease
Mycophenolate mofetil	Severe renal disease
IV immunoglobulin	Severe hematologic involvement
Rituximab	Severe disease refractory to treatment with cyclophosphamide

Adapted from [27] Habibi S, et al. Juvenile systemic lupus erythematosus: review of clinical features and management. Indian Pediatr. 2011;48(11):884

tis with rituximab as a combination therapy in treatment failure for patients with severe systemic disease.

Therapies for SLE are targeted to treat the affected organ systems and are usually coordinated by a rheumatologist. NSAIDs are used for arthritis and other musculoskeletal involvement. Systemic glucocorticosteroids are used in conjunction with DMARDs such as hydroxychloroquine to reduce the risk of side effects from steroid use in children, i.e., prednisone exceeding 0.2 mg/kg/day has been shown to result in growth retardation [32]. Hydroxychloroquine can cause ocular toxicity, more so in younger patients and when paired with other antimalarials. Methotrexate has shown benefit for arthritis and azathioprine and cyclophosphamide for lupus-associated nephritis [28]. Rituximab, an anti-CD20 monoclonal antibody, has been used in combination with some of the aforementioned therapies for treatment failures [33] (Table 40.3). Systemic corticosteroids in children with SLE often produce striae, both from the medication and from the associated weight gain (Fig. 40.3).

SLE in children is more severe than SLE in adults. SLE-associated nephritis causes 3 % of renal transplants in children, with a 5-year mortality of 22 % in those with end-stage renal disease, primarily due to cardiopulmonary complication or infections. While SLE was once universally fatal for children, now the mortality rate in developed countries is less than 10 % at 5 years, 14 % at 10 years, and 21 % at 15 years. However, in some developing nations such as Thailand, the mortality rate at 5 years is 27 % and at 10 years 36 %.

Experimental

Belimumab, a monoclonal antibody that acts as a B-cell activating factor inhibitor, was introduced in 2012 as a promising therapeutic agent in adults with SLE with autoantibodies. Currently, many other therapies are under development for adults and children suffering from SLE [36].

Childhood Discoid Lupus Erythematosus

Epidemiology/Demographics

- Cases have been reported in multiple ethnicities including African-American, Caucasian, Hispanic, and Middle-Eastern patients.
- Equal incidence in men and women.
- Rare disorder with only 80 reported cases reported in the literature as of 2008.

Ethnic and Racial Groups Affected [37–40]
African-American, Caucasian, Hispanic, Middle-Eastern

Childhood DLE is rare. In a 2008 literature review from the Netherlands only 80 cases had been reported, with an equal sex distribution [37]. There are reports in children from the Netherlands [38], in African-Americans and Hispanics [37, 39], and from Tunisia [40], among others.

Clinical Presentation

- Discoid lesions are erythematous plaques with follicular plugging often found on the face and scalp, which can result in atrophic scarring.
- The presence of discoid lesions on more than one body segment correlates with the development of systemic disease.
- A low incidence of photosensitivity has been reported in many cases, although a Tunisian study cited an 81 % incidence.

DLE (Fig. 40.4) may be present with erythematous plaques with follicular plugging, most often found on the face and scalp, and can resolve with atrophic scarring [38]. Discoid lesions presenting on more than one body segment in children is associated with systemic disease. Discoid lesions can be an early cutaneous manifestation of SLE. There is a higher rate of systemic involvement in children with DLE than in adults with DLE [2]. In a Tunisian study, there was a high incidence of photosensitivity in 81 % of cases while low incidences have been reported in other studies [39, 40]. The age of presentation of the reported 80 patients in the 2008 review was less than 10 years in half of patients and between 10 and 16 years in the other half [37]. Diagnosis by biopsy on the scalp with or without direct immunofluorescence can differentiate this form of alopecia from other scarring alopecias,

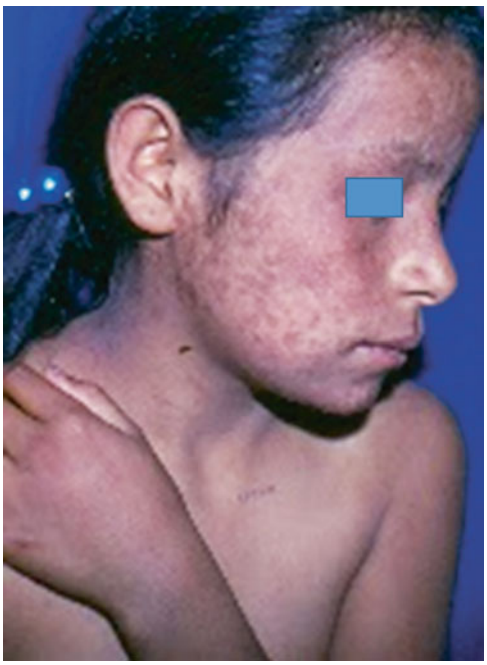

Fig. 40.4 Actinic prurigo (photo courtesy of Carola Duran-McKinster/Ramon Ruiz-Maldonado)

including kerion and morphea, and in teenagers, central centrifugal cicatricial alopecia (CCCA), a condition of follicular inflammation and degeneration noted to relate to aggressive styling techniques.

Treatment, Prognosis, and Ongoing Research

- Photoprotection with broad-spectrum sunscreen, photoprotective clothing, and sun avoidance.
- First-line therapy with high-potency topical or intralesional corticosteroids.
- Second-line therapy with hydroxychloroquine or oral corticosteroids.

Treatment for DLE without systemic involvement involves photoprotection and high-potency topical or intralesional corticosteroids. If necessary, oral corticosteroids or hydroxychloroquine can be tried, although clinicians should be aware of potential retinal toxicity and other complications [38, 41]. In other studies, thalidomide [42] and dapsone have been tried although hematologic and liver function abnormalities have been reported with dapsone [43]. In adults, years of treatment leads to resolution of lesions in half of patients [38]. A quarter of children with DLE develop SLE, as opposed to 6 % for adults with DLE. Long-term serologic monitoring for development of SLE is required in this subset of patients.

Experimental

In light of the success of calcineurin inhibitors in adults with DLE, these medications may have benefit in children but future studies are necessary [37] (Table 40.4).

Table 40.4 Treatments for discoid lupus erythematosus [37, 38, 41–43]

First-line	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance with high-potency topical or intralesional corticosteroids
Second-line	Oral corticosteroids or hydroxychloroquine; there are case reports with success using thalidomide or dapsone

Of note there can be associated retinal toxicity and cardiotoxicity with the use of hydroxychloroquine, although it has a safer cardiac profile than chloroquine [34]. *Use of dapsone has been associated with hematologic and liver function abnormalities* [41]

Idiopathic Photodermatoses

The idiopathic photodermatoses include actinic prurigo, hydroa vacciniforme, PMLE, and solar urticaria [44–47]. Actinic prurigo, hydroa vacciniforme, and PMLE are discussed in more detail here, given their higher incidence in skin of color.

Actinic Prurigo

Epidemiology/Demographics

- Actinic prurigo, also called hereditary or familial PMLE of Amerindians, is an autosomal dominant condition in Native American and Inuit children, with a prevalence of 1.2–8 %.
- Most often seen in Native American and Mestizo children, with reports of cases in Japan, Singapore, Australia, Continental Europe, and the United Kingdom.
- There is a reported 2–4:1 female:male distribution.

Ethnic and Racial Groups Affected [48–52]
Native American, Mestizo, Japan, Singapore, Australia, Continental Europe, and the United Kingdom

Actinic prurigo (also called hereditary or familial PMLE) is an autosomal dominant photosensitizing disorder in Native American and Inuit children with variable expressivity and reduced penetrance. The prevalence in these populations is reported between 1.2 and 8 % [50, 51]. It has also been reported in Caucasian Americans and African-Americans. Some authors contend that the onset of PMLE in childhood may suggest Native American heritage [52]. The incidence in Mexico is 1.5–3.5 %. Cases have also been reported in Japan, Singapore, Australia, Continental Europe, and the United Kingdom. The female to male ratio is 2–4:1 [48, 53, 54].

Clinical Presentation

- Pruritic erythematous papulonodular rash that may have a hemorrhagic crust or appear eczematous, traditionally in a photodistributed pattern, although nonexposed sites may be involved.

- In Native American children, oral and mucosal involvement such as conjunctivitis, pterygium, eyebrow hair loss, and cheilitis are often present.
- Rash can persist in patients the entire year in Central America but often presents in patients in the spring or summertime in northern latitudes.

Actinic prurigo is a pruritic erythematous papulonodular rash that may have a hemorrhagic crust or be eczematous. It is most prominent in a photodistributed pattern, although nonexposed sites may also be affected. Oral and mucosal involvement in Native Americans is often present with features such as conjunctivitis, hair loss from the eyebrows, pterygium, and cheilitis. The sole clinical finding in nearly a third of Mestizo children is cheilitis [49]. In Central America, the rash can persist in patients the entire year, whereas in more northern latitudes, it is most common in patients in the spring or summer [48, 55].

Treatment, Prognosis, and Ongoing Research

- First-line therapy with photoprotection and topical corticosteroids or topical tacrolimus with systemic corticosteroids as needed.
- Second-line therapy with PUVA or narrowband UVB (NB-UVB) desensitization.
- Third-line therapy with thalidomide. There is a risk of teratogenicity from this therapy.

Photoprotective clothing, sun avoidance, and broad-spectrum sunscreen are needed for prevention. Topical regimens such as corticosteroids and tacrolimus or systemic treatment with corticosteroids are beneficial. For serious cases, desensitization with PUVA or narrowband UVB a few times a week beginning at 50–70 % of the MED with incremental increases of 10 % can be tried. For refractory cases, systemic therapy with thalidomide for a few weeks until the condition resolves with a taper to the smallest maintenance dose possible [56]. Teratogenicity is a serious side effect in young females. Registry, contraceptive education, and frequent pregnancy testing should be performed in girls of child-bearing age. Other regimens including tetracycline, cyclosporine, azathioprine, vitamin E, beta-carotene, chloroquine, and pentoxifylline have been reported to be beneficial, but further study is necessary (Table 40.5). The condition may resolve with pitted scarring or postinflammatory hyperpigmentation but generally it persists into adulthood [48, 55]. Just as thalidomide, a medication with FDA approval for multiple myeloma and erythema nodosum leprosum, became a useful therapy for severe cases of actinic prurigo, novel applications of existing therapeutics may benefit children with these and other photosensitive disorders refractile to traditional treatments [57].

Table 40.5 Treatments for actinic prurigo [46, 49, 54]

First-line treatments	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance with topical or systemic corticosteroids or topical tacrolimus
Second-line treatments	Desensitization with PUVA or NB-UVB beginning at 50–70 % of the MED with incremental increases of 10 % as tolerated
Third-line treatments	Thalidomide for a few weeks until the condition resolves with a taper to the smallest possible maintenance dose

Other regimens with reported benefit include tetracycline, cyclosporine, azathioprine, vitamin E, beta-carotene, chloroquine and pentoxifylline, but further study is necessary

Hydroa Vacciniforme

Epidemiology/Demographics

- Reported in South Africans, Caucasians, Native Americans, Asians, and Hispanics.
- Equivalent male:female distribution, although females present with the disease earlier and males have a more prolonged disease course.
- Incidence of 1:300,000.

Ethnic and Racial Groups Affected [58–63]
Caucasian, Native American, South African, Asian, and Hispanic

Hydroa vacciniforme is a rare disorder that develops in children, sometimes in association with the Epstein–Barr virus (EBV). The incidence of the disorder is unknown but has been reported at 1:300,000, with an equal sex distribution in a review from Glasgow, although females presented with the disease earlier and males had a more prolonged disease course [64]. There have been reports of the disorder in South African, Caucasian, Native American, Asian, and Hispanic children [58–63].

Clinical Presentation

- Pruritic erythematous maculopapular and vesicular rash seen in a photodistributed distribution often on the face with perioral involvement. Umbilicated lesions or hemorrhagic crusting can also be observed
- The condition is often refractory to treatment but spontaneously resolves before adulthood. It may result in significant residual varioliform scarring.
- There can also be associated mosquito bite hypersensitivity and risk of lymphoproliferative malignancy in a distinct condition called hydroa vacciniforme-like lymphoma.

Hydroa vacciniforme clinically presents with a pruritic photodistributed erythematous maculopapular and vesicular rash that is often seen on the face with perioral involvement within hours to days after sun exposure. Umbilicated lesions and hemorrhagic crusting can be observed [64].

Treatment, Prognosis, and Ongoing Research

- Photoprotective clothing, broad-spectrum sunscreen, and photoprotection on windows in the home and vehicles.

Table 40.6 Treatments for hydroa vacciniforme [64–66]

Photoprotection	Broad-spectrum sunscreen, photoprotective clothing and photoprotection on windows in the home and vehicles
First-line treatment	Desensitization with NB-UVB although often refractory to treatment
Case reports with stated benefit	PUVA, antivirals, omega-3 fish oils, beta-carotene, hydroxychloroquine, chloroquine sulfate or the use of cyclosporine or azathioprine in severe cases

Of note there may be associated retinal toxicity and cardiotoxicity with the use of hydroxychloroquine and chloroquine [67]

- Desensitization with NB-UVB can serve as a useful adjunct, although the condition is often unfortunately refractory to therapy.
- Case reports of benefit from use of PUVA, antivirals, omega-3 fish oils, beta-carotene, antimalarials, cyclosporine, and azathioprine.

Hydroa vacciniforme is unfortunately oftentimes refractory to therapy. Photoprotective clothing, broad-spectrum sunscreen, and photoprotection on windows in the home and cars are recommended. Desensitization with narrowband UVB can serve as a beneficial adjunct [64]. There are case reports of benefit with other regimens, including antivirals such acyclovir and valacyclovir [65], PUVA, omega-3 fish oils, beta-carotene or antimalarials, and the use of cyclosporine or azathioprine in severe cases (Table 40.6). The condition often spontaneously resolves before adulthood but may result in significant residual varioliform scarring [66].

Recently, there has been a partition of hydroa vacciniforme cases into a typical subtype where cutaneous findings are limited to photodistributed sites versus a severe hydroa vacciniforme-like subtype with cutaneous findings that extend to photoprotected sites. This severe variant can be associated with high peripheral blood EBV DNA titers. A distinct condition called hydroa vacciniforme-like lymphoma has been associated with mosquito bite hypersensitivity and risk of lymphoproliferative malignancy [68]. Hydroa vacciniforme-like lymphoma is an EBV-associated T-cell and natural killer cell lymphoma, most commonly seen in children from Asia and South and Central America, associated with systemic manifestations including fever and hepatosplenomegaly [69, 70]. While some authors propose measuring the titers of EBV DNA, which may have utility in assessing a child's risk of malignant transformation and help direct the frequency and extent of clinical monitoring, it is important to reemphasize that hydroa vacciniforme-like lymphoma is a distinct clinical entity and that children with hydroa vacciniforme generally have a relatively benign clinical course.

Polymorphous Light Eruption

Epidemiology/Demographics

- No reliable cross-sectional studies have been performed but the condition in adults is generally more common in fair-skinned individuals.
- However, certain subtypes of PMLE are characteristic in skin of color such as the pinpoint variant.
- Traditionally it has been taught that the incidence of PMLE is inversely related to latitude, with reported incidences of 22 % in Scandinavia, 10–20 % in North America and Western Europe, 5 % in Australia, 1 % in Singapore, and 0.56 % in India.

Ethnic and Racial Groups Affected [47, 71–77]
All racial groups and ethnicities, including African-Americans, Caucasians, Native Americans, Hispanics, Asians, Indians

PMLE is the most common idiopathic photodermatosis, often presenting in young women [71, 78]. No reliable cross-sectional studies have been performed but the condition is generally more common in fair-skinned individuals. However, certain variants of PMLE are characteristic in skin of color. It has traditionally been taught that the incidence is inversely related to latitude, with reported incidences of 22 % in Scandinavia, 10–20 % in North America and Western Europe, 5 % in Australia, 1 % in Singapore, and 0.56 % in India [71–74]. However, this relationship to latitude was not demonstrated in a 2010 multicenter study conducted from Greece to Scandinavia in 6,850 patients. This study showed an 18 % prevalence overall, with a prevalence of 22 % in women and 9.8 % in men, respectively. In general, the prevalence of PMLE was highest in Fitzpatrick skin type I, 33.4 % in women and 28.6 % in men, with a decline in Fitzpatrick skin type IV to 11.2 % in women and 4.0 % in men. Interestingly, the lowest prevalence was 13.6 % in Turku and the highest prevalence was 19.5 % in Athens, the cities with the highest and lowest latitudes respectively in this study [75].

In a study done in India of 362 photosensitive adult patients with Fitzpatrick skin types IV to VI, nearly 60 % had PMLE with the papular subtype identified in 37 %, pinpoint in 31 %, eczematous in 22 %, lichenoid in 5 %, and plaque-variant in 4 % [44]. Pinpoint PMLE is the most prominent variant in African-Americans and has also been observed in Native Americans and Asians [47, 76, 77].

Clinical Presentation

- Erythematous papules, vesicles, urticaria, or plaques that may appear eczematous.
- Pinpoint variant in children of color is characterized as 1–2 mm papules in a photodistributed distribution

without involvement of flexural areas or the face that can appear like lichen nitidus.
- Juvenile spring eruption is another variant seen in children on the face, ears, and dorsal hands during spring; more common in boys due to short haircuts.

PMLE can variably present as an acute and possible recurrent eruption of erythematous papules, vesicles, or plaques that may appear eczematous presenting within hours to days after significant sun exposure. The clinical presentation and pathology of the pinpoint variant can appear like lichen nitidus with 1–2 mm papules in a photodistributed distribution without involvement of flexural areas or the face [76]. Juvenile spring eruption is a variant seen in children on the face, ears, and dorsal hands during the spring. It is more common in boys, felt to be due to less inherent photoprotection due to short haircuts [79].

Treatment, Prognosis, and Ongoing Research

- Photoprotection typically leads to resolution of the rash in the pinpoint variant of PMLE in children and juvenile spring eruption within weeks without scarring.
- Topical corticosteroids can be tried if there is pruritus with desensitization using PUVA or NB-UVB starting at 70 % of the MED with incremental increases of 10–20 % as tolerated or a brief course of systemic steroids. Topical polypodium leucotomos in sunscreens or in an oral form enhance photoprotection.
- For refractory cases, benefit has been reported with administration of cyclosporine, azathioprine, and antimalarials with equivocal results reported with beta-carotene and nicotinamide.

The pinpoint variant of PMLE in children and juvenile spring eruption typically resolves with sun avoidance in a few weeks without scarring. Topical corticosteroids can be tried for symptomatic relief if there is associated pruritus. For prevention of future episodes, photoprotective clothing, sun avoidance, and broad-spectrum sunscreen are necessary. The intensity of the rash lessens during the summer due to recurrent exposure in a process referred to as *hardening*. For a patient who expects to have a period of significant sun exposure, desensitization with PUVA or NB-UVB a few times a week for the preceding month starting at 70 % of the MED with incremental increases of 10–20 % as tolerated or a brief course of systemic steroids can be beneficial. Topical polypodium leucotomos in sunscreens or administered in an oral form also provide photoprotection [71, 80]. In refractory cases, there have been equivocal results from the use of oral beta-carotene and nicotinamide. Cyclosporine or azathioprine have reportedly been tried with benefit. Antimalarial drugs have been beneficial, including hydroxychloroquine, which should be used with careful blood monitoring and periodic ophthalmologic screening. Medications like chloroquine and canthaxanthine should be avoided due to greater potential for ocular side effects (Table 40.7) [78, 80, 81]. While some patients will have PMLE reactions for life, three-quarters of patients in one study experienced remission or improvement over a 32-year period [82]. Ongoing research is improving the clinical management of PMLE. To illustrate, one randomized, controlled, double-blind study showed that there were improved clinical outcomes with the concomitant use of avobenzone and ecamsule as UVA filters in an SPF 40 sunscreen as opposed to use of a single agent [83].

Table 40.7 Treatments for polymorphous light eruption [71, 78, 80–82]

First-line therapy	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance typically leads to resolution of the rash within weeks without scarring
Second-line therapy	Topical polypodium leucotomos in sunscreens or administered in an oral form has been beneficial. Topical corticosteroids can be trialed if there is pruritus with desensitization using PUVA or NB-UVB starting at 70 % of the MED with incremental increases of 10–20 % as tolerated or a brief course of system steroids
Third-line therapy	Reports of benefit using cyclosporine, azathioprine and antimalarials with equivocal results reported with beta-carotene and nicotinamide in the literature
Of note there can be associated retinal toxicity and cardiotoxicity with the use of antimalarials [67]	

Genetic and Metabolic Conditions

Genetic and metabolic conditions associated with photosensitivity are numerous, including Hermansky-Pudlak Syndrome (HPS), Bloom syndrome, helicase defects, including Rothmund–Thomson syndrome, trichothiodystrophy, Werner's syndrome, Cockayne syndrome, Kindler syndrome, xeroderma pigmentosum, ultraviolet sensitive syndrome, albinism, Hartnup disease, Smith–Lemli–Opitz syndrome, phenylketonuria, hepatic porphyrias (i.e. porphyria cutanea tarda, variegate porphyria, hereditary coproporphyria, hepatoerythrocytic porphyria), and erythropoietic porphyrias (i.e. congenital erythropoietic porphyria and erythropoietic protoporphyria) [1, 80]. There are some differences in racial prevalences among these disorders. A retrospective review of the incidence of porphyrias in African-Americans and Caucasians were 0.7 % and 21.4 %, respectively. This may be due to the higher incidence of hereditary hemochromatosis in Caucasians and its role in the development of sporadic porphyria cutanea tarda [47].

The clinical presentation and management strategies for HPS and certain subtypes of oculocutaneous albinism (OCA) are discussed here owing to their higher prevalence in children of color [46, 84, 85].

Hermansky–Pudlak Syndrome

Epidemiology/Demographics

- Reported in many ethnic groups but most prevalent in Puerto Rico, Madras in the East Indies, and the Netherlands.
- The incidence of HSP is 1:1,800 and the carrier rate of the mutated *HSP1* gene is 1:22 in northwest Puerto Rico.
- As of 1990 there were 400 individuals in that region with the mutated *HSP1* gene and a projected 200 other individuals with the disorder worldwide.

Ethnic and Racial Groups Affected [84–97]
All races and ethnic groups, most prevalent in Puerto Rico, Madras in the East Indies, and the Netherlands, with reports in Americans including African-Americans and in Honduras, Venezuela, El Salvadore, Uruguay, Cuba, Mexico, Continental Europe, United Kingdom, Japan, China, and India

HPS is an autosomal recessive disorder due to a defect in vesicle formation, affecting the function of lysosomes, platelet dense bodies, and melanosomes that presents at birth and is most prevalent in children from Madras in the East Indies, Netherlands, and Puerto Rico [84, 85, 98]. There are nine subtypes of the disorder [86]. The incidence of HSP in northwest Puerto Rico is 1:1,800 and the carrier rate of the mutated *HSP1* gene on chromosome 10q23 is 1:22. The same mutation is found in a community in the Swiss Alps and five other loci are known. As of 1990, there were 400 individuals in that region with the mutated *HSP1* gene and a projected 200 individuals who share the other mutations worldwide [83, 84, 86, 98]. Since that study was published, there have been reports of cases in Honduras, Venezuela, El Salvadore, Uruguay, Cuba, and Mexico [89]. There are also reports on boys and girls from Israel [90, 91], Continental Europe [90, 92, 93], United Kingdom [90], Japan [85, 93, 94], China [94], India [95], and the United States [96], including children of African-American descent [97].

Clinical Presentation

- Hypopigmentation of the skin, eyes, and hair with pigmented nevi and the development of basal cell carcinomas, actinic keratosis, and squamous cell carcinomas.
- Ophthalmologic findings include photophobia, poor visual acuity, nystagmus, foveal hypoplasia, and strabismus.
- Granulomatous colitis, pulmonary fibrosis, and cardiomyopathy can develop from the phagocytosis and collection of ceroid in the pulmonary, gastrointestinal, and cardiac tissue.

A hemorrhagic diathesis and oculocutaneous albinism result from respective defects in platelet dense bodies and melanosomes [87, 99]. There is hypopigmentation of the skin and eyes, with red-brown to cream colored diluted hair color [89]. Pigmented nevi and the development of basal cell carcinomas, actinic keratosis, and squamous cell carcinomas can be observed on exam with petechiae and ecchymoses due to the hemorrhagic diathesis. Bleeding gums, epistaxis, and menorrhagia may also be noted. Ophthalmologic findings include photophobia, poor visual acuity, nystagmus, foveal hypoplasia, and strabismus. Granulomatous colitis, pulmonary fibrosis, and cardiomyopathy can develop from the phagocytosis and collection of ceroid in the pulmonary, gastrointestinal, and cardiac tissue [98].

Treatment, Prognosis, and Ongoing Research

- Photoprotection with broad-spectrum sunscreen, photoprotective clothing, and sun avoidance and not using medications that inhibit prostaglandin synthesis such as aspirin is recommended.
- Topical thrombin and systemic vasopressin may be needed for surgical procedures and platelet infusions considered if the patient sustains trauma.
- Regular skin cancer screenings are important.

Treatments for children suffering from this disorder include sun-protection measures and not using medications that inhibit prostaglandin synthesis such as aspirin. Topical thrombin and systemic vasopressin may be needed for surgical procedures and platelet infusions considered if the patient sustains trauma. Regular skin cancer screenings are also important [87]. Other management considerations include pulmonary function testing, baseline chest X-ray, ophthalmologic screening, colonoscopy, and other testing as needed with subspecialist involvement [98] (Table 40.8). The leading causes of mortality in this disorder include the inherent bleeding diathesis, enteropathic complications from granulomatous colitis and restrictive lung disease [87]. Recent research has demonstrated that the interstitial lung disease in HSP may result from the deposition of galetin-3, a beta galactoside-binding lectin for which HSP-1 has a regulatory role [100].

Table 40.8 Treatments for Hermansky–Pudlak syndrome [87, 98, 100]

Organ system	Management considerations
Skin	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance; skin-cancer screenings due to the risk of basal cell carcinoma and squamous cell carcinoma
Hematologic	Do not use aspirin or other prostaglandin inhibitors; thrombin and systemic vasopressin may be needed for surgical procedures and platelet infusions considered if the patient sustains trauma
Ophthalmologic	Ophthalmologic screenings with photoprotection for photophobia and treatment for foveal hypoplasia or other complications as needed
Pulmonary	Baseline chest X-ray and if needed pulmonary function testing
Gastrointestinal	Colonoscopy if indicated

Oculocutaneous Albinism

Epidemiology/Demographics

- Incidence of OCA2 is 1:15,000 among those of African descent while the incidence of the brown phenotypic variant of OCA2 is 1:3,900–10,000 with a high prevalence among patients of African descent and Native Americans.
- In African-Americans, the incidence of OCA3 is 1:10,000 while in Nigeria the incidence is 1:1,100 among the Ibgo.
- The highest incidence of OCA is 1 % among the Kuna tribe.

Ethnic and Racial Groups Affected [84, 98, 101–104]
African descent, Native American, Caucasian, Asian, Hispanic

There are four forms of OCA. African children have the highest incidence of oculocutaneous albinism type 2 (OCA2). OCA3 is most common in Black children in South Africa. The most common OCA in Japan is OCA4 [101, 105, 106]. OCA2 is the most prevalent form of OCA. Incidence of OCA2 is 1:15,000 among those of African descent while the incidence of the brown phenotypic variant of OCA2 is 1:3,900–10,000, with a high prevalence among patients of African descent and Native Americans.

In the Navajo population, the prevalence of OCA2 in one study was 1:1,500–2,000, with a carrier rate of 4.5 % [102]. Another review of the disorder in Amerindians notes a prevalence rate of 1:28–6,500 among different Amerindian populations [103]. In African-Americans, the incidence of OCA3 is 1:10,000 while in Nigeria the incidence is 1:1,100 among the Igbo [101]. The highest incidence of OCA is 1 % among the Kuna tribe [84, 98].

Clinical Presentation

- OCA2, OCA3, and OCA4 are characterized by mild to moderate hypopigmentation of the hair, eyes, and skin.
- In the brown phenotypic variant of OCA2, the irides can be hazel or blue-gray with yellow hair while in OCA3 the irides can be hazel, blue, or brown with ginger-colored hair.
- As patients age, some pigmentation may develop with freckling and darkening of the hair, eyes, and skin in these subtypes of OCA.

Clinically these autosomal recessive disorders are characterized by mild to moderate hypopigmentation of the hair, eyes, and skin. There is a range of phenotypes associated with OCA2. In those of African descent with the brown variant of OCA2, the irides can be hazel or blue-gray with yellow hair. One percent of patients with Prader–Willi or Angelman syndromes have OCA2. The phenotype in OCA4 has similarities to that of OCA2. In OCA3, there may be brown, hazel, or blue irides with reddish-brown skin and ginger-colored hair. As patients with these subtypes of OCA age, some pigmentation may develop with freckling and darkening of the hair, eyes and skin. Poor visual acuity, foveal hypoplasia, nystagmus, and strabismus are possible ophthalmologic findings in both disorders although often less severe in OCA3 [84, 98, 104, 107, 108].

Table 40.9 Treatments for oculocutaneous albinism [84, 98, 107, 108]

Photoprotection	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance
Clinical monitoring	Dermatologic and ophthalmologic examinations every 6 months
Ophthalmologic management	Use of an eye patch for strabismus, contact lenses or surgery for nystagmus and eyeglasses for poor visual acuity with tinted lenses for photophobia

Treatment, Prognosis, and Ongoing Research

- Photoprotection with broad-spectrum sunscreen, photoprotective clothing, and sun avoidance.
- Dermatologic and ophthalmologic examinations every 6 months.
- Use of an eye patch for strabismus, contact lenses or surgery for nystagmus, and eyeglasses for poor visual acuity with tinted lenses for photophobia.

Photoprotection is of great importance. The development of malignant melanoma in a patient with oculocutaneous albinism has been reported [109], in addition to nonmelanoma skin cancers. Children should have dermatologic and ophthalmologic examinations every 6 months. For strabismus an eye patch can be used. Contact lenses or surgery are used to manage nystagmus. Visual acuity can be improved through the use of eyeglasses, with tinted lenses for photophobia, to correct refractive errors (Table 40.9) [84, 107, 108]. As stated above, individuals with these forms of OCA may gain more pigment with age. Visual findings may improve over time [98]. As the pathobiology of these disorders is further elucidated, in particular, the genetic underpinnings regulating maturation and trafficking of tyrosinase, the development of innovative therapeutic options will be possible [110].

Nutritional Deficiencies

Epidemiology/Demographics

- Seen internationally with reports among African-Americans, Caucasians, Africans, Asians, Hispanics, and others, secondary to lack of fortified foods or a diet limited to maize or corn.
- Highest prevalence for children under 5 years of age 60.8 million and 12.3 million children in India and China respectively.
- Highest mortality rate in South Africa at 2.28 deaths per million inhabitants, with Venezuela and Brazil having the highest mortality rates thereafter.

Ethnic and Racial Groups Affected [3, 74, 111]
African-American, Caucasian, Africans, Asians, Hispanics

Pellagra is a nutritional deficiency due to a cellular scarcity of niacin caused by insufficient dietary intake or impaired gastrointestinal absorption of nicotinic acid and tryptophan. Iatrogenic cases due to use of drugs like isoniazid or chloramphenicol are possible as is an association with carcinoid syndrome. There was an epidemic in America at the turn of the nineteenth century predominately among African-Americans. In South Carolina in 1912, 30,000 cases were reported with a mortality rate of 40 %. The disorder is still seen in developing countries but the incidence is fortunately declining [74]. Regions at risk include those without fortified foods or a diet limited to maize or corn. According to a study from UNICEF, in children under 5 years of age the countries with the highest prevalence of pellagra are India and China with 60.8 million and 12.3 million children affected respectively. Outbreaks have been reported in Nepal, Angola, Mozambique, and other regions recently. At a clinic in Transvaal in South Africa, half of the patients had pellagra. According to a 2004 report from the World Health Organization, worldwide the death rate from pellagra was highest in South Africa at 2.28 deaths per million inhabitants, with Venezuela and Brazil having the highest rates thereafter [3, 111] (Table 40.10).

Clinical Presentation

- Clinical manifestations of pellagra can include dermatitis, dementia, and diarrhea.
- Erythematous patches or thin plaques with scale in a photodistributed distribution that may be accompanied by oral mucosal involvement.
- The presence of this rash on the upper chest is known as *Casal's necklace.*

The clinical manifestations of pellagra include dermatitis, dementia, diarrhea, and death. The rash presents as erythematous patches or thin plaques with scale in a photodistributed distribution that may blister. The presence of this rash on the upper chest is referred to as *Casal's necklace*, which heralds the name of the Spaniard who first described this condition in 1735. Hyperplasia of sebaceous glands is also seen. Oral mucosal involvement is present in a third of patients with fissures, angular cheilitis and ulcerations. On bony prominences there is hyperpigmentation and thickening of skin [3, 111].

Table 40.10 Treatments for pellagra [3, 111, 112]

Photoprotection	Broad-spectrum sunscreen, photoprotective clothing and sun avoidance
Supplementation and dietary management	Supplementation with nicotinic acid and diet rich in proteins and vitamin B complex

Treatment, Prognosis, and Ongoing Research

- Photoprotection with broad-spectrum sunscreen, photoprotective clothing, and sun avoidance.
- Supplementation with nicotinic acid.
- Diet rich in proteins and vitamin B complex.

Treatment includes supplementation with nicotinic acid with a diet rich in proteins and vitamin B complex [3, 111]. Interesting recent research in Kyoto has shown increased levels of prostaglandin E2 in mice with niacin deficiency leads to the development of reactive oxygen species, which increase cutaneous inflammation and contributes to photosensitivity. The group used a cyclooxygenase inhibitor-2 to successfully treat photosensitivity in mice without the side effects commonly associated with niacin supplementation such as flushing [112]. This may serve as a novel therapeutic approach to pellagra.

Exogenous Causes

Exogenous causes of photosensitivity include phytophotodermatitis and drug-induced photosensitivity. Phytophotodermatitis is a phototoxic reaction frequently seen in tropical regions due to UVA exposure following contact with psoralens in plants. This can result in postinflammatory pigment changes in ethnic skin. There are many drugs known to cause photosensitivity, including NSAIDs, tetracyclines, fluoroquinolones, retinoids, psoralens, and seizure medications like carbamazepine [74, 80, 113].

Photoaggravated Conditions

For the purposes of this chapter on photosensitive disorders, photoaggravated conditions are not discussed in detail, but a few defining features of disorders with distinguishing features in children of color are discussed briefly. Photoaggravated conditions include atopic dermatitis, psoriasis, seborrheic dermatitis, Darier's disease, herpes simplex, acne vulgaris, rosacea, pityriasis rubra pilaris, and dermatitis herpetiformis, among others [3, 44, 55].

Atopic Dermatitis

Atopic dermatitis (AD) is the most frequent dermatologic condition in children with a greater prevalence in females. It presents as either photosensitive AD or AD with PMLE. In phototesting, there is a normal MED in AD with PMLE whereas the MED is lower in photosensitive AD [3]. There is a higher incidence and severity of AD in skin of color with a six times greater incidence in blacks and a two times greater

incidence in Asians as compared to whites. It presents with a pruritic rash on the face and extensor surfaces in infants and flexural areas in children. Erythema may be more difficult to appreciate in children of color. Features more often seen in children of color include circumoral pallor, Dennie–Morgan folds, prominent ankle and dorsal hand lichenification, pityriasis alba, and follicular eczema with marked pruritus. Prolonged traditional or alternative treatment regimens may be necessary in children of color. Topical tacrolimus is used for pityriasis alba with benefit also seen from use of pimecrolimus and low-potency topical corticosteroids. Mid-potency topical corticosteroids are necessary for follicular eczema. In general, treatments for mild to moderate disease includes emollients, topical corticosteroids and immunomodulators such as tacrolimus and pimecrolimus, topical or systemic antibiotics, phototherapy, systemic corticosteroids, and antihistamines used in moderate to severe disease. For treatment failure, immunosuppressive medications and other agents have been tried. Sequelae of AD observed in children of color include postinflammatory pigment changes [3, 44, 105, 114]. Photoprotection in photoaggravated cases should include fragrance-free sunblocks, hats, sun glasses, and lightweight sun-protective clothing. Photoprotection should also be used to allow children with dyspigmentation to have natural improvements in their skin tone, which might be otherwise enhanced with irregular tanning.

Psoriasis

Psoriasis is seen in all ethnicities with a worldwide prevalence of 2 %. The incidence of psoriasis is higher in Caucasian Americans than African-Americans but a distinguishing feature in African-Americans is circumferential Woronoff's rings around psoriatic plaques with less evident erythema and more obvious postinflammatory pigment change. The psoriatic plaques may look violaceous and there may be more hyperkeratotic plaque involvement of the palms and soles in skin of color. An oil-based preparation of topical fluocinonide that is left in overnight is a useful adjunct to other shampoos used for scalp psoriasis due to the inherent drying of hair that can occur from frequent hair washing. Treatments for psoriasis include mid-potency topical corticosteroids, calcipotriene, anthralin, and tar preparations with NB-UVB, and tacrolimus used as second-line agents and systemic regimens, including cyclosporine, methotrexate, etanercept, and acitretin used for children with widespread involvement. Tazarotene gel can be used for nail psoriasis. There are special considerations in particular ethnic groups like a vitamin D polymorphism in Japanese and Turkish patients that limits response to calcipotriol [105, 115–117]. Photoaggravated psoriasis should be treated with strict sun protection and enhanced topical care in lieu of phototherapeutic care.

Seborrheic Dermatitis

Seborrheic dermatitis is likewise seen in children of all races and is characterized by erythematous plaques with greasy scale on the scalp, face, and intertriginous regions with seborrhea petaloides with an annular configuration seen in ethnic skin. Postinflammatory pigment changes are again an unfortunate sequela in skin of color. While daily use of shampoos such as ketoconazole, zinc pyrithione, ciclopirox, and selenium sulfide are often recommended for scalp involvement, these agents can potentially damage tightly coiled or chemically treated hair. These prescription medications can be applied to the scalp once or twice weekly for 15 min then rinsed out with use of a shampoo with conditioner thereafter. Topical corticosteroids with a foam vehicle are also recommended for scalp involvement. In African-American adults, a few weeks of treatment with pimecrolimus has improved facial hypopigmentation seen in seborrheic dermatitis, although relapse has been noted in a Korean study within weeks of treatment cessation [118]. However, the medication has not been tried in children and use in infants is discouraged. Other agents that have been used include topical ketoconazole or corticosteroids [105, 117, 119]. Photoaggravation of seborrheic dermatitis may be via enhanced visualization of hypopigmentation in children of color. When this occurs, strict sun avoidance should occur until inflammation of the skin has adequately resolved.

Summation/Conclusion

There is a wide breadth of dermatologic disorders in children that are associated with photosensitivity. This spectrum includes collagen vascular diseases, idiopathic photodermatoses, genetic and metabolic disorders, nutritional deficiencies, exogenous causes, and photoaggravated conditions. Within these subclasses, lupus erythematosus, actinic prurigo, hydroa vacciniforme, PMLE, HPS, and particular subtypes of OCA are more prevalent in children of color. Understanding of the diagnostic criteria, review of the associated features, and collaboration with rheumatologists, cardiologists, nephrologists, and gastroenterologists may be required for adequate care of these unusual patients.

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Actinic Prurigo

41

Sonia Toussaint-Caire

Abstract

Actinic prurigo (AP) is a chronic photodermatosis that occurs mainly in dark-skinned populations with strong Amerindian genetic lineage who live in dry and sunny geographical areas at altitudes over 1,000 m above sea level. AP usually begins in childhood and is more frequent in women. Expression of HLA-DR4 and subtype DRB1*0407 have been found to be related with the disease. Pathogenesis may be related to the production of tumor necrosis factor alpha (TNF-α) by epidermal keratinocytes, after UVB radiation. Patients usually have lesions on sun-exposed skin, characterized by extremely pruritic erythematous macules, papules, and infiltrated plaques. Due to intense scratching, excoriations, lichenification, scars, and residual hypo or hyperpigmentation may be seen. Affectation of lips and conjunctiva is a very characteristic manifestation of the disease. Microscopic study of vermillion border biopsy shows a very distinctive inflammatory infiltrate with lymphoid follicle formations. Main differential diagnosis includes photosensitivity associated with atopic dermatitis. Besides adequate photoprotection, thalidomide is the first line medical treatment with excellent results, although significant side effects should be closely monitored and prevented.

Keywords

Actinic prurigo • Photodermatosis • Cheilitis • Thalidomide

Introduction

Actinic prurigo (AP) is an inflammatory, chronic, and idiopathic photodermatosis. As its name implies, skin lesions are photodistributed. Labial and/or conjunctival mucosae can be affected too, and in more severe cases, the cutaneous rash may extend to areas not exposed to sun. AP is predominantly seen in dark-skinned populations with a strong Amerindian genetic lineage [1] (Fig. 41.1).

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It was first described in 1952 by López González from Argentina, under the name of Solar Prurigo [2]. Few years later, in 1954, Escalona and coworkers reported the first cases in Mexico [3], and from then on, AP has been identified in other latitudes such as Canada and in Central and South America [1]. Dr. Fabio Londoño, from Colombia, was the one who coined the term "actinic prurigo" [4].

Epidemiology

- **Begins in childhood between 6 and 8 years of age and is more common in women.**
- **Commonly seen in dark-skinned people, Fitzpatrick's phototypes IV and V.**
- **Patients usually live in high-altitude, dry, sunny geographical areas.**

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AP occurs mainly in children between 6 and 8 years of age [5, 6] but can be seen at any age group [6]. It is more common in women, with a ratio of 2:1 compared to men [5–7] and commonly affects people with darker skin phototypes (IV and V of Fitzpatrick's classification) [5, 6, 8] who live in dry and sunny geographical areas located in high altitudes, usually above 1,000 m above sea level. However, there have been cases reported to occur in people living at lower altitudes, even at sea level [5, 6].

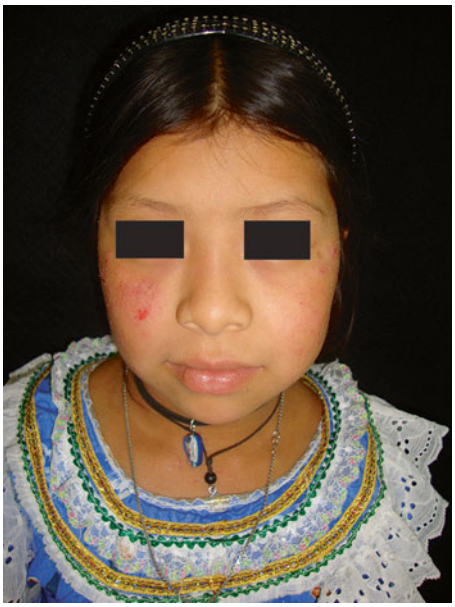

Fig. 41.1 Young girl from the Tojolabal community from the State of Chiapas, Mexico, with early lesions of actinic prurigo (AP)

Pathophysiology

Genetic Amerindian ancestry plays an important role in the pathogenesis of the disease [9], and may explain why AP predominates in countries, like Guatemala, Colombia, Honduras, Ecuador, Peru, Bolivia Mexico, that have indigenous populations with low cross-cultural influence, where there is a reported prevalence of the disease of 3.9 % [10] (Fig. 41.2).

Isolated cases have been reported in Costa Rica, Venezuela, Argentina, Uruguay, Chile, northern United States, in Canada's Inuit population [1, 5, 7] (prevalence of 0.1 %) [10], Australia, Great Britain, and Thailand [1].

Little is known about the exact etiology of this disease. Some identified factors involved are low socioeconomic status, family history [8], living in rural areas, continuous contact with farm animals and exposure to wood smoke [11].

Regarding genetic predisposition, it has been shown that, in Mexico, 90–92.8 % of patients with AP express HLA-DR4 [12–15] and the allele HLA-DRB1*0407 [1, 7, 10] the most common subtype (60–80 %) [12, 15].

HLA-DR4 has also been identified in European patients with AP [1, 10]. Other related alleles associated with the disease are HLA-A28 and B39 in Mexico [1, 7], HLA-A24, HLA-Cw4, and DRB1*14 in Canada [7, 10], HLA-Cw4 in Chimila indians from Colombia [16], and HLA-B40 and Cw3 in Bogota [1, 7, 10].

Increased expression of HLA-B40 and Cw3 is seen in populations with strong Amerindian genetic lineage and may explain why this disease is more common in this ethnic group [1, 17]. HLA subtype DRB1*0407 has also been found to be more frequent in Colombian patients with AP [18].

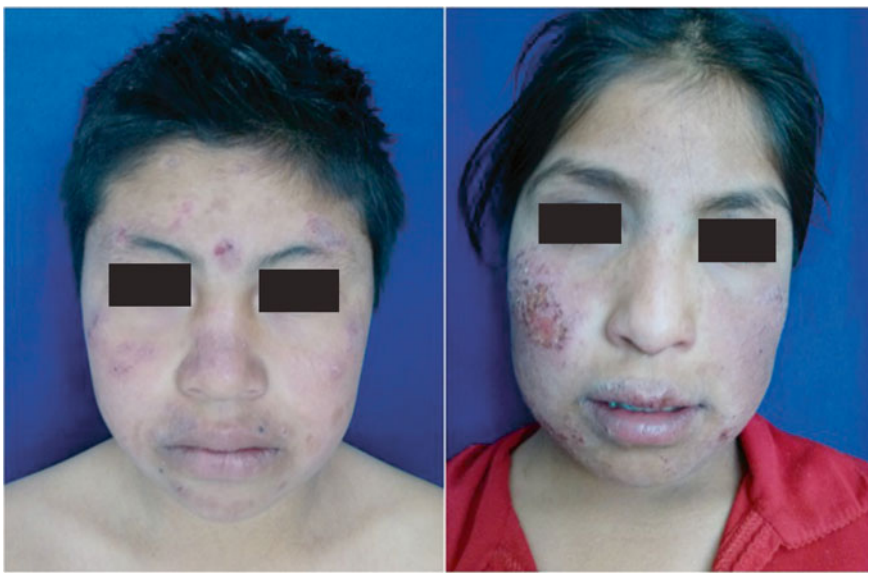

Fig. 41.2 Well-developed lesions of AP in two patients from the Mazahua community from the State of Mexico, Mexico

In 1984, Moncada and coworkers [19] suggested that the skin of patients with AP had an abnormal immune response characterized by an increased number of T lymphocytes in peripheral blood, especially T helper cells (CD4+), and also an increased number of CDIa+ dendritic cells in the dermal inflammatory infiltrate [5, 20]. It was subsequently observed that this abnormal response was induced by solar radiation, particularly the spectrum of ultraviolet radiation A (UVA) and B (UVB). However, visible light also has an important role in the pathogenesis of the disease [1, 5, 21].

UVB radiation stimulates the production of tumor necrosis factor alpha (TNF-α) by epidermal keratinocytes, especially those from the suprabasal layer [1, 6]. This cytokine is able to activate immunoreactivity and expression of adhesion molecules on keratinocytes, which promote the migration of inflammatory cells that produce epidermal tissue injury and necrosis [6, 22]. TNF-α also initiates the activation of transcription factor NF-κβ and programmed cell death (apoptosis), so it is very likely that this immune response occurs in the pathophysiology of AP [23].

B cells in lymphoid follicles express CD80 (B7) and promote proliferation of Th2 cells that release IL-5 (eosinophil activator) and IL-4 (which stimulates production of IgE [24] and the activation of mast cells). This process promotes the formation of the characteristic ectopic germinal centers (lymphoid follicles) on the lips, also documented in other conditions of hypersensitivity, autoimmunity, or infection [25].

On the other hand, lymphocytes T-CD4+ induce the synthesis of IL-2, which activates natural killer cells and promotes the production of IgE antibodies [1] that have been demonstrated in situ and in serum of patients with AP [26].

Mast cells also play an important role in both inflammatory and allergic reactions. In 2007, a Mexican study has shown a higher density of mast cells in the lip lesions of patients with AP, compared to normal and inflamed mucosa due to other pathologic processes [26].

The presence of increased levels of IgE, eosinophils, and mast cells suggests a hypersensitivity reaction as one of the mechanisms in the pathophysiology of AP [25]. Generally, hypersensitivity reactions occur after exposure to an antigen that activates effector cells. AP may be classified as a delayed hypersensitivity reaction [19, 27, 28] type IVa, because after sun exposure, keratinocytes are able to produce TNF-α [1, 6]. It can also be regarded as IVb type reaction due to the presence of increased levels of IgE, eosinophils, and mast cells [29–31].

Clinical Presentation

- **Polymorphous dermatitis affecting photoexposed areas of face, neck, trunk, and extremities.**
- **Lesions consist of extremely itchy erythematous macules, papules, infiltrated plaques. excoriations, lichenification, scars, and residual hypo or hyperpigmentation**
- **Characteristically, it affects lips and conjunctiva with eventual pseudopterygium formation.**

AP is a polymorphous photodermatosis. Patients usually have lesions on sun-exposed skin of face, neck, trunk, and extremities, and the lesions are distributed in a bilateral and symmetrical array (Fig. 41.3). This dermatosis predominates over areas where radiation hits with more intensity, such as nasal dorsum, zygomatic and superciliary arches, lower lip, and conjunctiva [5, 12]. Less frequently, lesions can be observed in non-photoexposed skin [9, 15] (Fig. 41.4).

AP is an inflammatory dermatosis characterized by erythematous macules and papules that converge to form infiltrated plaques. Because it is extremely itchy, there are also

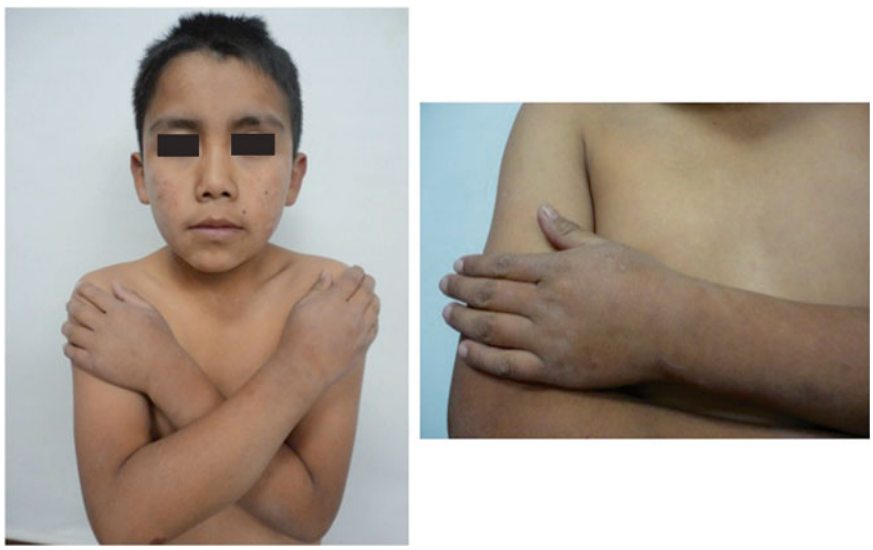

Fig. 41.3 Patients with AP usually have lesions on sun-exposed skin of face, neck, trunk, and extremities and show a bilateral and symmetrical distribution. Associated xerosis can be seen

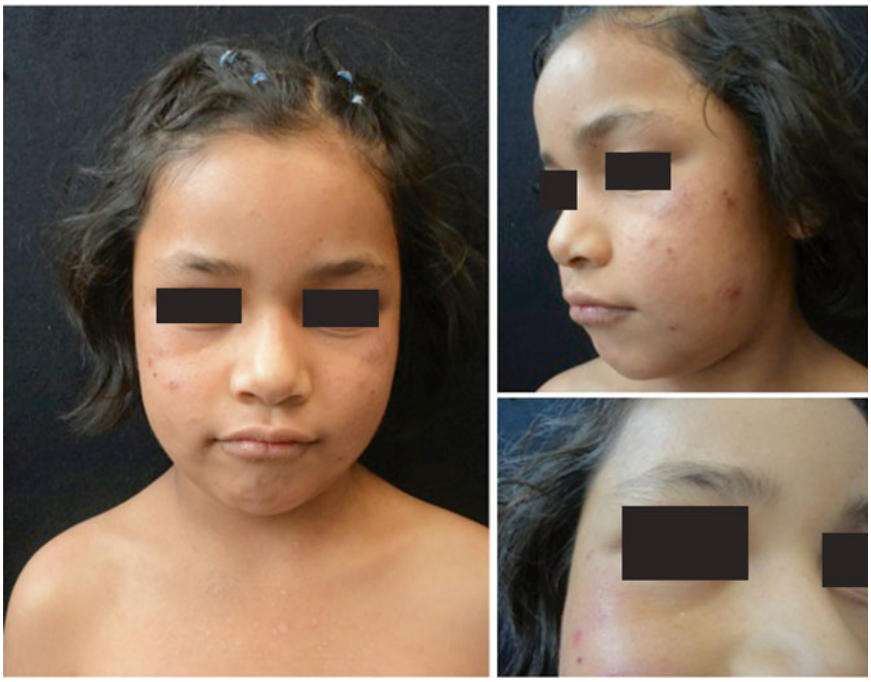

Fig. 41.4 Mild AP. Lesions predominate over nasal dorsum, zygomatic and superciliary arches, lower lip, and conjunctiva. Hypopigmented residual lesions can be seen

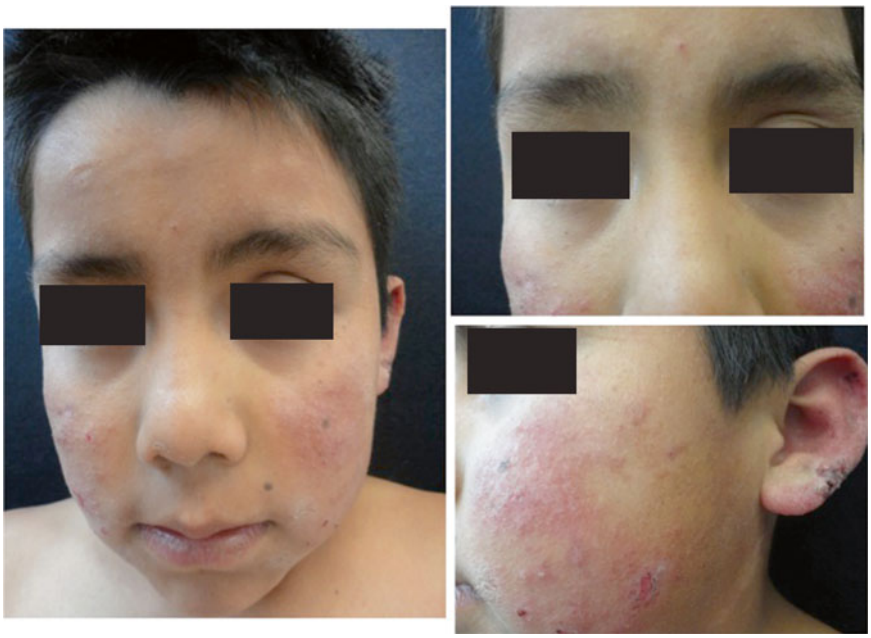

Fig. 41.5 Moderate to severe AP. Papular lesions become confluent forming infiltrated plaques. There are more exulcerations covered with scale crusts and lichenified areas, due to severe scratching

excoriations, scale-crusts, lichenification, scars, and residual hypo or hyperpigmentation [5–7, 9, 12] (Fig. 41.5).

On the vermilion border of the lips, erythema, edema, fissures, and ulcers covered by serohemorrhagic scales can be observed. This is a very characteristic manifestation of the disease and is referred to as actinic prurigo cheilitis (APC). There is sometimes associated gingival hypertrophy, possibly secondary to mouth breathing due to the uncomfortable symptoms on the lip [12]. APC is a common clinical manifestation and more frequently affects the lower lip. Up to 65 % of children with AP can show labial lesions [1], and in 27.6 %, it could be the only manifestation of the disease [12] (Fig. 41.6).

Conjunctiva can be affected in approximately 45 % of patients. Conjunctivitis of AP initially presents with hyperemia, photophobia, increased tearing, and subsequent pseudopterygium formation, and in severe cases, there can be partial loss of the visual fields. It appears that conjunctival alterations are usually a late manifestation of the disease [5, 9, 12] (Fig. 41.7).

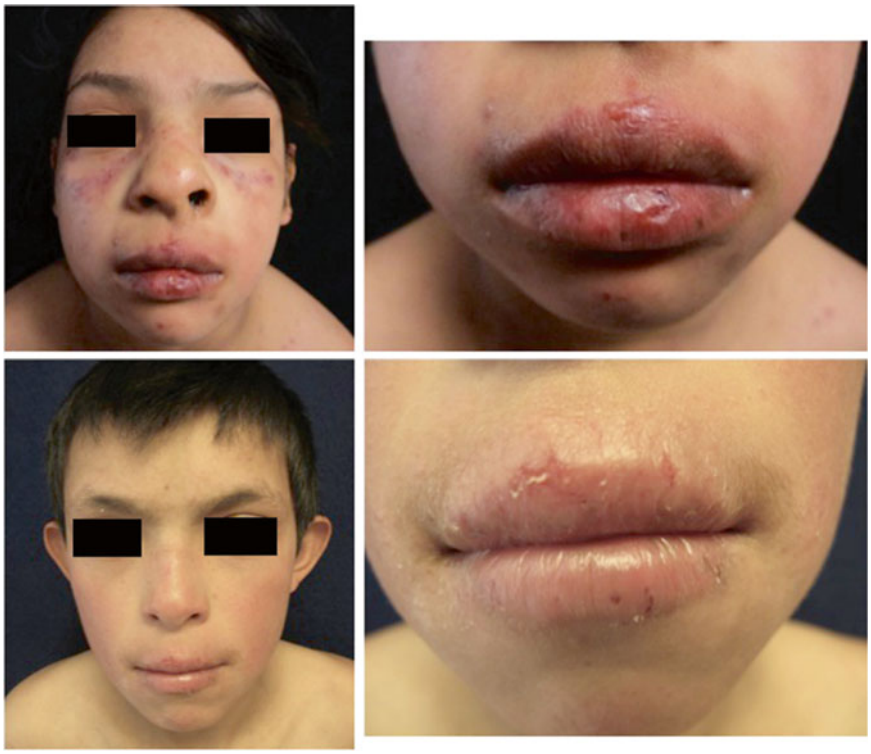

Fig. 41.6 Actinic prurigo cheilitis. Lips can be swollen, with areas of erythema, fissures and ulcers covered by serohematic scales

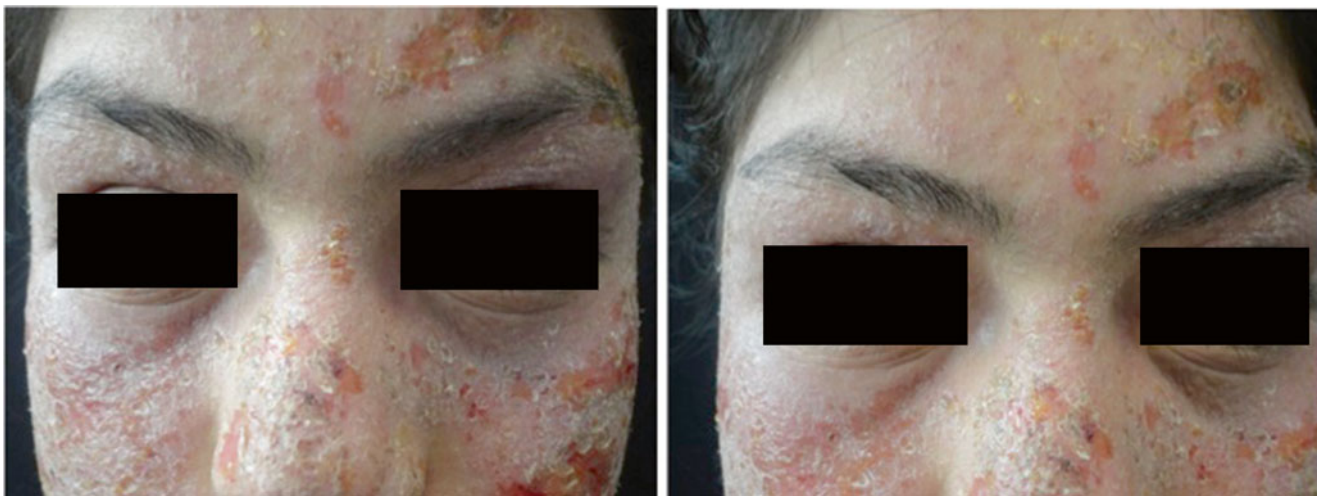

Fig. 41.7 Actinic prurigo conjunctivitis. Conjunctivitis of AP initially presents with hyperemia, photophobia, increased tearing and subsequent pseudopterygium formation

AP has a chronic clinical course with frequent exacerbations after sun exposure. In geographical areas where seasons are well defined, flares usually occur during spring and summer and decrease in the fall [9, 15]. In contrast, in regions with tropical climate without marked seasonal variations, exacerbations may occur year-round related with constant exposure to sunlight [5].

Histopathology

The microscopic picture of skin lesions shows hyperkeratosis, foci of parakeratosis, acanthosis, thickening of the basement membrane, and a superficial perivascular inflammatory infiltrate of lymphocytes. Sometimes, there are only mild inflammatory changes with epidermal hyperplasia, suggestive

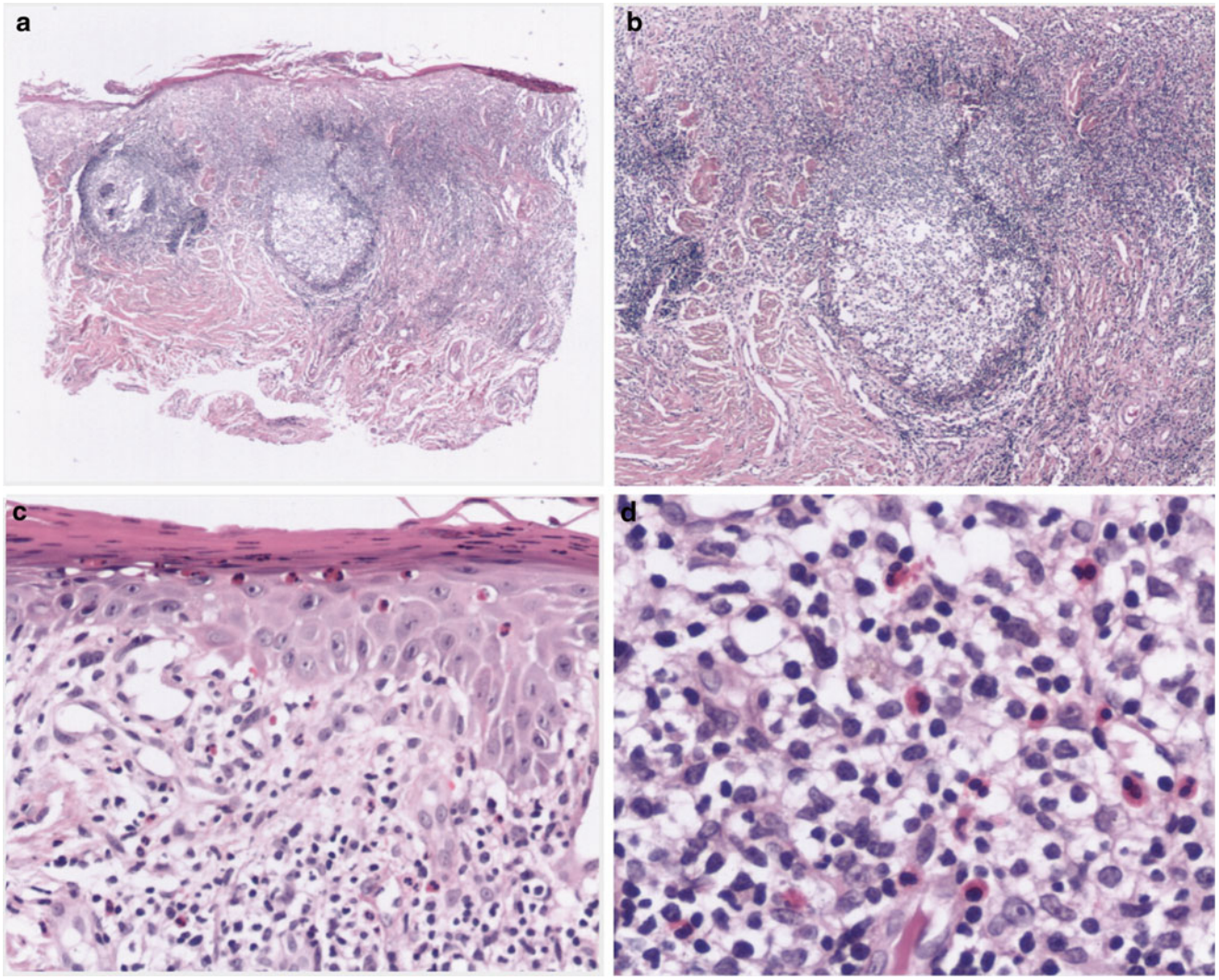

Fig. 41.8 Histopathology of AP. (**a**) Low power view of a vermillion mucosa biopsy that shows a nodular lymphocytic infiltrate in the lamina propria. (**b**) Higher power magnification of the ectopic lymphoid follicle characteristic in cheilitis of AP. (**c**) Epithelial spongiosis, exocytosis of eosinophils and dermal inflammation. (**d**) Mixed inflammatory infiltrate with lymphocytes, histiocytes, eosinophils and plasma cells

of a chronic dermatitis; however, the presence of an intense nodular inflammatory lymphocytic infiltrate with numerous eosinophils and mast cells suggests the diagnosis [32]. Unlike other photodermatoses, adnexal structures are not affected and solar elastosis is not a common finding.

Histology of APC shows hyperkeratosis, scale crusts covering ulcerated areas, mild acanthosis, spongiosis, and mild vacuolar alteration of the basal layer. At the superficial portion of the submucosa, eosinophils and melanophages can be found, and deeper in the lamina propria, there are dilated capillary vessels, interstitial edema, and a band-like or nodular lymphocytic infiltrate. Lymphocytes may aggregate and form well-defined ectopic lymphoid follicles. This particular histologic picture is named "follicular cheilitis" and is a very characteristic feature of APC [12] (Fig. 41.8).

Conjunctival lesions show epithelial hyperplasia alternating with atrophy, vacuolation of the basal layer (60 %), capillary dilation, and an inflammatory lymphocytic infiltrate with eosinophils and melanophages in the lamina propria. Lymphocytes may also have a follicular arrangement as in the labial mucosa [5, 7].

Lymphoid follicles can be found in up to 80 % of vermillion border or conjunctival mucosa biopsies [1, 5, 12].

Immunohistochemical studies of the inflammatory infiltrate in skin lesions have demonstrated a predominantly T lymphocyte CD45RO+ population (memory T cells) and expression of interleukin-2 (IL-2) [1, 6, 33]. It has also been reported that ectopic lymphoid follicles of lip biopsies are formed in the periphery by T lymphocytes (CD45+, IL-2), and in the center, by B (CD20+) lymphocytes [5, 7]. There

are also numerous eosinophils and abundant extracellular deposits of IgM, IgG, and C3 in the papillary dermis [6, 7].

Diagnosis

The diagnosis of AP is mainly a clinical one and can be supported by histopathological study [34] preferably of the vermillion mucosa, where ectopic lymphoid follicles are more commonly found [32].

Differential Diagnosis

The main clinical differential diagnoses of AP include: atopic dermatitis with photosensitivity, photocontact chronic dermatitis, chronic actinic dermatitis, and polymorphous light eruption (PMLE) [7, 9]. The major diagnostic challenge is atopic dermatitis with photosensitivity as it also begins in childhood, is a chronic dermatitis and very often patients are unaware of their atopic status [35].

PMLE is also a seasonal related idiopathic photodermatosis. It is more frequently seen in African Americans and Caucasians [36] while in Amerindian indigenous populations, is very rare.

PMLE also differs from AP because its onset is sudden and it can last hours to days and then subsides. Unlike AP, lesions in PMLE can be painful, and patients may experience flu-like symptoms. Skin lesions range from papules, plaques, and papulovesicles. Vesicles are never found in AP patients [9]. The characteristic mucosal lesions of the vermillion border and conjunctiva are not seen in PMLE. Histolopathology of PMLE is characterized by an almost exclusive lymphoid infiltrate with marked dermal edema. Eosinophils and mast cells frequently seen in AP are rarely found in PMLE.

Conjunctivitis of AP should be differentiated from vernal conjunctivitis, which is bilateral, recurrent, pruritic, and highly prevalent in adolescents with a previous history of atopy [37].

The most important clinical differential diagnosis of APC is traumatic cheilitis secondary to lip biting, where there is erythema, atrophy, erosion, and areas of postinflammatory hyperpigmentation. There is also burning sensation and tendency to chronicity [38]. It is important not to confuse the terms of APC and actinic cheilitis, as they are completely different entities [39].

Treatment

As the first-line treatment, it is essential to avoid sun exposure and the appropriate use of sunscreen. Medical treatment can be used depending on the extent and severity of the disease [7, 12, 40]. Therapeutic options include topical or systemic corticosteroids, vitamin E, β-carotenes, tetracyclines, antimalarials, antihistamines, cyclosporine A (topical calcineurin inhibitor), and low doses of UVA or UVB phototherapy. All of these treatment modalities may induce partial remissions [5, 12, 41].

Thalidomide is a glutamic acid derivative [42]. It was proposed as an optional treatment for AP in 1973 by Londoño [43], who demonstrated excellent results when treating patients with AP. These findings were confirmed in 1975 by Saul [44, 45] and in 1993 by Vega-Memije et al. [17]. Currently, this is the most effective medical treatment [7, 34] for AP, because it is an immunomodulator that inhibits TNF-α [6] and IFN [46] (Figs. 41.9 and 41.10).

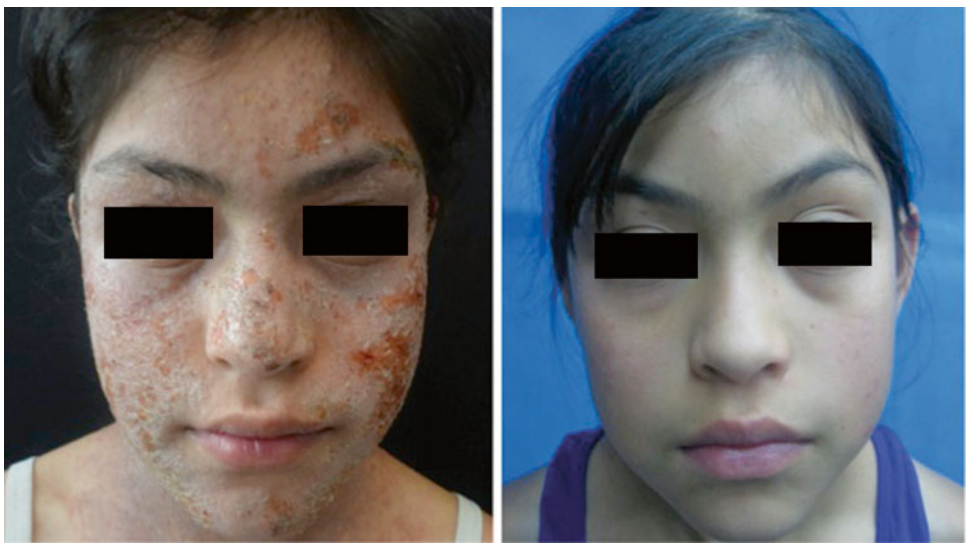

Fig. 41.9 Excellent results after 2 months of treatment with oral thalidomide. Skin and conjunctival lesions are almost resolved

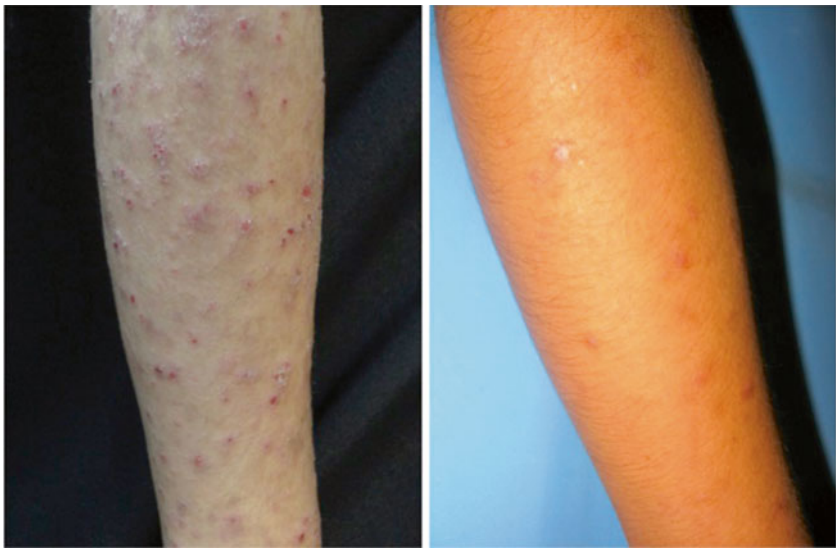

Fig. 41.10 Markedly reduced papular lesions on upper extremities after treatment with thalidomide

The effective oral dose of thalidomide reported for children from 9 to 16 years is 0.5–2.5 mg/kg/day [47] and in adults the initial dose is 100–200 mg daily and this can be maintained until clinical improvement is observed [7, 12, 46], which usually occurs between 2 and 4 weeks after treatment onset [12]; it can subsequently be decreased to a minimum effective dose usually of 25 mg per week [7, 12].

The main adverse effect of thalidomide is teratogenicity, making mandatory the use of effective contraception for all women in the reproductive age [7, 12]. Other reported side effects include drowsiness, increased appetite [7], headache, nausea, constipation, skin hypersensitivity [1], and sensory neuropathy [7]. The latter can be seen in 91 % of the patients even when asymptomatic, so it should be confirmed by nerve conduction studies [48].

Conclusions

AP is a chronic photodermatosis most commonly seen in dark-skinned populations with a strong Amerindian genetic lineage. Conjunctival and vermillion mucosae are characteristically affected in AP and are a clue to make the differential diagnosis between other photodermatoses. Distinctive histological findings include ectopic lymphoid follicles in the biopsies of lip mucosa and a mixed inflammatory infiltrate with eosinophils.

Currently, thalidomide is the most effective medical treatment, although with significant adverse effects.

There is still much to know about the genetics and pathogenesis of AP. More research studies are needed to fully understand this disease.

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Part IX

Collagen Vascular and Inflammatory Skin Diseases

Collagen Vascular Disease: Cutaneous Lupus Erythematosus

42

Saez-de-Ocariz Marimar and Orozco-Covarrubias Luz

Abstract

Cutaneous lupus erythematosus may present with acute, subacute, and chronic lesions. It affects all races, but children of color are at greater risk of developing cutaneous lupus. Acute cutaneous lupus erythematosus may produce mid-facial or disseminated lesions and is a common feature of systemic lupus erythematosus (SLE). Subacute cutaneous lupus erythematosus is characterized by psoriasiform and/or annular lesions. Neonatal lupus erythematosus refers to a clinical spectrum of cutaneous, cardiac, and systemic abnormalities in newborn infants whose mothers have autoantibodies to Ro and La antigens. Chronic cutaneous lupus erythematosus is typically characterized by discoid lesions, but other varieties can be observed. The diagnosis of cutaneous lupus erythematosus is clinical, but may be aided by skin biopsy. Treatment mainly consists of strict photoprotection and mid-high potency topical corticosteroids. Follow-up is mandatory since all forms of cutaneous lupus erythematosus may progress to SLE, especially among children of color.

Keywords

Lupus erythematosus • Subacute • Neonatal • Discoid • Autoantibodies • Photoprotection

Neonatal Lupus

Introduction

- **Clinical spectrum of cutaneous, cardiac, and systemic abnormalities in newborns through 6 months of life**
- **Transplacental passage of autoantibodies against Ro/SSA, La/SSB, and ENA/U1-RNP**
- **Skin manifestations usually benign and self-limited**

Neonatal lupus erythematosus (NLE) refers to a clinical spectrum of cutaneous, cardiac, and systemic abnormalities observed in newborns due to transplacental passage of autoantibodies against Ro/SSA, La/SSB, and, less commonly, U1-ribonucleoprotein (ENA/U1-RNP) from their mothers [1]. The most common presentation is nonscarring, nonatrophic skin lesions that resemble subacute cutaneous lupus erythematosus (SCLE). The infants may have no skin lesions at birth but develop them during the first weeks of life. Cardiac, hematological, hepatobiliary, central nervous, and pulmonary systems may also be involved. The condition is usually benign and self-limited, but sometimes may be associated with serious sequelae [2].

Epidemiology

- **No apparent racial predilection**
- **Female to male ratio is 2:1 for cutaneous lesions, equal for cardiac disease**
- **15–30 % incidence of congenital heart block in infants with NLE**

NLE is a rare acquired autoimmune disease that occurs in 1:20,000 live births in the United States [2]. Elsewhere, epidemiology is usually described in small case series, reporting

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three new cases per year in China [3] and one new case per year at a University Hospital in Taiwan [4]. NLE is seen in less than 2.5 % of infants born to mothers with the described autoantibodies. The presence of certain major histocompatibility complexes such as HLA B8 and HLA DR3 in the mother predisposes the infant to NLE and congenital heart block [5].

There is no apparent racial predilection [4–8], but disparity in outcomes between minorities (with higher case fatalities) and whites has been observed [7]. The female to male ratio is approximately 2:1 regarding cutaneous NLE, but gender distribution for cardiac disease is approximately equal [9].

The risk of NLE or congenital heart block developing in the child of a woman who tests positive for Ro/SSA but has never had a child with NLE or congenital heart block is less than 1 %. However, the risk increases significantly if the mother has had previous children with NLE or congenital heart block [10].

The incidence of congenital heart block is 15–30 % in infants with NLE. Heart block usually develops *in utero* between the 18th and 24th weeks of pregnancy. Infants born to mothers with hypothyroidism due to thyroid antibodies and anti-Ro/SSA seropositivity are at nine times higher risk of developing congenital complete heart block than infants born to mothers with only anti-Ro/SSA seropositivity [10].

Approximately 40–60 % of mothers are asymptomatic when the infants are diagnosed to have NLE. The remaining may have SLE, Sjogren syndrome, rheumatoid arthritis, or undifferentiated autoimmune disorder. Mothers with primary Sjogren syndrome or undifferentiated autoimmune syndrome have a greater risk of delivering an infant with congenital complete heart block than those with SLE [11].

Clinical Features

- **Dermatologic, cardiac and hepatic abnormalities are the most common features**
- **Skin lesions resemble those of SCLE**
- **Periorbital erythema is a very common clinical feature**

The most common clinical manifestations of NLE are, in decreasing order of frequency, dermatologic, cardiac, and hepatic abnormalities [1, 2, 4, 6]. Some infants may also have hematologic, neurologic, or splenic abnormalities [2–4, 6]. One or more systems may be involved.

Cutaneous lesions may be present at birth but often appear within the first few weeks of life [12, 13]. Annular, erythematous, or polycyclic plaques with or without fine scales, similar to those of SCLE, characterize NLE and appear predominantly on the scalp, neck, or face (typically periorbital in distribution), but similar plaques may appear on the trunk or extremities (Fig. 42.1) [6, 12]. Induction of skin lesions by sun exposure can occur for up to 3 months postpartum.

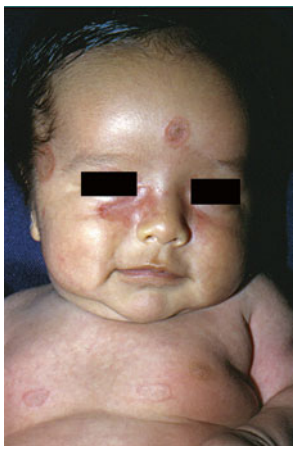

Fig. 42.1 Annular, erythematous, scaly plaques in the face and trunk of a neonate with NLE

Periorbital erythema, referred to as "raccoon eye" or "owl eye," is a very common characteristic [6]. At times, the lesions may be urticarial, desquamative, ulcerative, or crusted [6, 14]. Bullous lesions may be seen with a particular predilection for the soles of the feet [14]. In some infants, solar exposure seems to precipitate the eruption [15]. These lesions typically last for weeks or up to 6 months and then resolve spontaneously consequent to the disappearance of maternal antibodies in the neonatal circulation [12]. Dyspigmentation is frequent but it may resolve spontaneously. Atrophic lesions and, rarely, atrophic scars may develop [6, 13]. Telangiectasia is often prominent and is the sole cutaneous manifestation reported in some patients. The atrophic telangiectatic changes are most evident near the temples and scalp and do not necessarily occur in the same sites as the erythematous lesions [12]. The latter site may occasionally be associated with a permanent alopecia. Telangiectasia, scarring, and atrophic changes are expected to persist.

The cardiac manifestations include conduction abnormalities (first-, second-, and third-degree heart block) and cardiomyopathy [1, 2, 16]. Third-degree heart block, once established, is usually irreversible [4]. Congenital heart block may present as bradycardia noted *in utero* or during physical examination at birth. Conduction disturbances may also present as irregular heartbeat and prolongation of the QT interval. Congenital heart block may be associated with endocardial fibroelastosis and cardiomyopathy [1]. In some cases, myocarditis and pericarditis can develop which may lead to bradycardia. Heart failure is a well-recognized complication during the neonatal period.

Hepatobiliary involvement may present with elevation of liver enzymes (such as aspartate aminotransferase and alanine aminotransferase) and/or conjugated hyperbilirubinemia occurring a few weeks or months after birth and resolving thereafter. Some infants may have mild hepatomegaly and, less commonly, splenomegaly [1]. The hepatomegaly and splenomegaly are usually transient. Cholestatic hepatitis and hepatic failure may also rarely occur [17].

Hematologic disturbances (e.g., hemolytic anemia, thrombocytopenia, and neutropenia) may occur in the first 2 weeks of life. Infants with hematological involvement are usually asymptomatic [1]. Autoantibodies, mainly anti-Ro, bind directly to the neutrophil and cause neutropenia. Thrombocytopenia may manifest as petechiae. Hematologic symptoms usually appear at around the second week of life and disappear by the end of the second month. Lymphopenia is not a characteristic hematologic abnormality of NLE [12].

Other abnormalities such as hydrocephalus and macrocephaly may occur [18]. Aseptic meningitis and myelopathy have rarely been reported [6]. Pneumonitis may manifest as tachypnea and/or tachycardia [1].

Pathogenesis

- **Anti-52/60-kDa Ro/SSA and anti-48-kDa La/SSB antibodies are associated with heart block**
- **Anti-50-kDa La/SSB antibodies are associated with cutaneous disease**
- **Anti-ENA/U1RNP antibodies are usually associated with atypical cutaneous features and thrombocytopenia**

NLE is caused by the transplacental passage of maternal autoantibodies [2, 3]. Approximately 98 % of the affected infants have maternal transfer of autoantibodies against Ro/SSA, La/SSB, and, less commonly, ENA/U1-RNP.

The antibodies associated with heart block and with cutaneous disease are believed to be different; antibodies against the 52/60-kDa Ro/SSA and 48-kDa La/SSB ribonucleoproteins are associated with heart block, whereas antibodies against the 50-kDa La/SSB ribonucleoprotein are associated with cutaneous disease [11]. Ultraviolet radiation and estrogens increase Ro antigen expression on the surface of the keratinocytes [1].

The 52-kDa Ro/SSA (Ro52) ribonucleoprotein is an antigenic target strongly linked with the autoimmune response in mothers whose children have NLE, congenital heart block, and other conduction abnormalities [1]. Anti-Ro52/SSA autoantibodies antagonize the serotonin-induced L-type calcium channel activation on human fetal atrial cells and trigger an inflammatory response, leading ultimately to fibrosis and scarring of the atrioventricular node, sinus node, and His bundle [6].

Anti-ENA/U1RNP autoantibodies are usually associated with atypical cutaneous lesions without cardiac or systemic abnormalities in a small number of NLE cases and may play a role in the pathogenesis of thrombocytopenia [6].

In addition to its presence in the skin and heart, the Ro antigen is also found in the liver, bowel, lungs, brain, and blood cells—the tissues that are most often affected by NLE [1]. However, only some neonates exposed to these autoantibodies develop complications. Therefore, other factors such as titers of maternal antibodies, genetic predisposition, and environmental factors such as viral infection may be involved [19].

Diagnosis and Differential Diagnoses

- **Diagnosis depends on clinical features on the infant and the demonstration of NLE-associated antibodies in maternal serum**
- **Skin biopsy is useful when the diagnosis is in doubt**
- **Several differential diagnoses include seborrheic dermatitis, epidermolysis bullosa, atopic dermatitis, and tinea corporis among others**

The diagnosis is usually established based on the clinical features and the demonstration of NLE-associated antibodies in the serum of the mother or the affected infant. Screening of infants with NLE for the presence of these antibodies is strongly recommended [2, 4, 6].

Skin biopsy is useful in patients with NLE when the diagnosis is in doubt. Histologic examination shows interface dermatitis, keratinocyte damage, moderate hyperkeratosis, follicular plugging, and vacuolar degeneration in the basal cell layer. Epidermal atrophy may be found. Inflammatory infiltrate may be intense with bulla formation histologically. An immunofluorescent examination reveals a granular IgG deposition at the dermoepidermal junction; IgM and C3 deposition may also be evident [12].

Laboratory investigations may reveal pancytopenia, thrombocytopenia, leukopenia, or elevated transaminase levels [20].

Differential diagnosis of NLE includes seborrheic dermatitis, atopic dermatitis, neonatal acne, epidermolysis bullosa, tinea corporis, psoriasis, granuloma annulare, erythema multiforme, Langerhans cell histiocytosis, congenital rubella, congenital syphilis, Bloom syndrome, and Rothmund–Thomson syndrome [20].

Treatment

- **Photoprotection and topical steroids for cutaneous lesions**
- **Evaluation of pacemaker need for cardiac lesions**
- **Systemic steroids or immunosuppressive agents for severe systemic involvement**

Photoprotection and low-potency topical corticosteroids are the mainstay of therapy for cutaneous lesions of NLE. Parents of the affected children must be thoroughly counseled

regarding avoidance of sunlight, proper use of sunscreen, and protective clothing [21].

Sometimes, though there is resolution of active skin lesions, pigmentary changes, atrophy, and telangiectasia may persist over the face and other exposed body parts. In such cases, cosmetic camouflage helps these children in social interaction. Persistent telangiectasia may be managed with vascular laser [21].

Systemic corticosteroids or immunosuppressives are not recommended to treat cutaneous lesions of NLE. In rare cases, if systemic therapy is indicated, hydroxychloroquine may be used [21].

Patients with NLE with cardiac involvement require regular monitoring to assess cardiac function and the need for a pacemaker. A pacemaker is often necessary for those who are unable to compensate for a slow heart rate. Serial echocardiography to monitor for a prolonged PR interval should also be arranged. If the cardiac involvement is severe, activity may have to be restricted in the young child [21].

Infants with severe hepatic and hematological involvement may require treatment with systemic corticosteroids, intravenous immunoglobulin, and/or immunosuppressive agents [6].

Children with NLE need continued follow-up, especially before adolescence and if the mother herself has an autoimmune disease [22]. Although the child may not be at increased risk of developing SLE, the development of some form of autoimmune disease in early childhood may be of concern. As many mothers are unaware of their diagnosis at the time of the child with NLEs birth, mothers must be advised to seek work up and clinical management of their systemic disease, as well as guidance regarding future pregnancies.

Prognosis

The morbidity and mortality of NLE of childhood depend on the organ systems affected [2, 3]. Children with NLE have an excellent long-term outcome when only skin lesions are present [16, 23]. The cutaneous lesions usually disappear by 6 months of age, coincident with the clearance of maternal antibodies from the child's circulation [2]. Involvement of the skin may, rarely, lead to scar formation. Although children with cutaneous disease may be more prone to develop SLE or autoimmunity later in life, this is mainly due to their genetic predisposition, not that they had NLE. Their unaffected siblings are also at risk for development of SLE or autoimmunity. While the cutaneous lesions of NLE are themselves benign, cutaneous NLE is associated with a 6–10-fold risk for a subsequent child with cardiac NLE [2, 16, 23].

NLE with cardiac involvement is associated with a 20–30 % mortality rate in the neonatal period [2, 16]. Mortality is particularly high in cases of congenital heart block with concurrent cardiomyopathy [7, 12]. Death most often results from congestive heart failure caused by congenital heart block. Approximately 57–66 % of patients with congenital heart block eventually require a pacemaker [2, 16, 23]. Those with pacemakers are at risk of developing dilated cardiomyopathy in their lives [1]. However, many children with congenital heart block may be relatively asymptomatic until adolescence, when they begin to exercise. At that time, they may develop syncope and require a pacemaker implantation. Prospective clinical trials on the use of antenatal fluorinated steroids in women with anti-SSA/Ro and/or anti-SSB/La antibodies and fetuses with heart block identified *in utero* are required before definitive recommendations can be made. A number of anecdotal cases support the use of dexamethasone for treatment of hydrops and possibly incomplete block [2].

Most patients with NLE affecting liver or blood have transient disease that spontaneously resolves within 4–6 months. In some cases, cholestatic hepatitis and liver failure may occur, which is associated with a poor prognosis [1]. Anemia, thrombocytopenia, and neutropenia are self-limited. However, if severe thrombocytopenia is present, internal bleeding can lead to a poor prognosis [1].

Ongoing Research

Currently, the main focus of the investigation in NLE lies on the search for reliable markers that predict the specific involvement of fetal organs and for a safe and effective treatment to prevent definitive lesions [24].

Conclusion

NLE refers to a clinical spectrum of cutaneous, cardiac, and systemic abnormalities observed in newborn infants whose mothers have autoantibodies against Ro/SSA and La/SSB. The condition may be associated with serious sequelae. Neonates with NLE should be managed at a tertiary care center, and multidisciplinary team involvement may be indicated.

Cutaneous Lupus Erythematosus

Introduction

- **Lupus erythematosus is a complex autoimmune disease with variable clinical features**
- **Cutaneous lupus erythematosus (CLE) can be classified as acute, subacute, and chronic**
- **All forms of CLE may progress to SLE**

Lupus erythematosus (LE) is a complex autoimmune disease that generates a chronic, persistent multiorgan inflammatory process with variable clinical features and course. CLE can be classified as acute, subacute, which includes neonatal lupus, and chronic [25, 26]. Acute CLE may produce mid-facial or disseminated lesions and will be discussed in another chapter as it is a common feature of SLE. SCLE was first described in 1979 by Sontheimer et al. [27] as a distinct subset of cutaneous lupus clinically characterized by psoriasiform and/or annular lesions. Chronic cutaneous lupus erythematosus (CCLE) is typically characterized by discoid lesions, but other varieties can be observed [26]. All forms of CLE may progress to SLE [25].

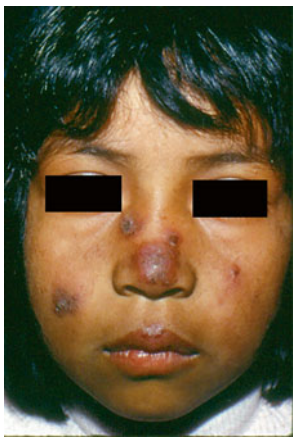

Fig. 42.2 Localized DLE lesions on the face of a Mexican Mestizo patient

Epidemiology

- **SCLE is extremely rare in childhood and female predominance is noted among the reported cases**
- **Less than 3 % of patients develop discoid lupus erythematosus (DLE) before the age of 10 years**
- **Female predominance in DLE patients might depend on the age of onset**

SCLE is extremely rare in childhood though a few cases have been reported in literature. Among the described cases, there is a frank female predominance (2.5:1) and the mean age at diagnosis is 6.6 ± 3.7 years [28–34].

DLE is uncommon in childhood (with around 80 published cases) [35–46] and exceptional in infancy [40, 46]. Less than 3 % of patients with DLE develop the disease before the age 10 years [40]. Some authors note the absence of female predominance [40, 46] whereas others have noted a female predominance, more marked in patients less than 10 years (5:1) than in older than 10 years (1.5:1) of age [41].

Clinical Features

- **SCLE is characterized by annular or psoriasiform photodistributed lesions**
- **DLE is the most common form of CCLE and may present with a linear arrangement**
- **Lupus tumidus, lupus panniculitis, and chilblain lupus may not exhibit epidermal involvement**

Subacute Cutaneous Lupus Erythematosus

This type of cutaneous lupus is typically photosensitive, with lesions confined to sun-exposed skin. Despite this fact, mid-facial skin is usually spared, while the sides of the face, V of the neck, and extensor aspects of the upper extremities are commonly involved. SCLE lesions may have an annular configuration, with raised red borders and central clearing, or a papulosquamous presentation (either eczematous or psoriasiform in appearance). Lesions often heal without scarring but with long-lasting hypopigmentation or even vitiligo-like leukoderma and telangiectases [28–34]. Nail dystrophy affecting almost all the nails has been described by Rai and Balachandran [30]. Although the classic presentation is in the form of annular or papulosquamous lesions, poikilodermatous [47], erythrodermic [48], and bullous SCLE [49] have also been reported in adults.

Patients with SCLE can complain of mild systemic symptoms (the most prominent of which are musculoskeletal complaints); however, approximately one half of them fulfill the criteria for SLE as *per* the American Rheumatism Association criteria, although it is usually a milder form of the disease [30].

Chronic Cutaneous Lupus Erythematosus

The term CCLE encompasses several variants of cutaneous lupus: DLE, LE tumidus, lupus panniculitis, and chilblain lupus, DLE being the most common form among these [26].

Discoid Lupus Erythematosus

DLE lesions are found most often on the face, scalp, and ears, but may be present in a widespread distribution [50]. Occasionally, DLE lesions may appear on mucosal surfaces, including the lips, nasal mucosa, conjunctivae, and genital mucosa [51].

DLE consists of erythematous plaques with atrophy, scale, alopecia, follicular plugging, and telangiectasias (Fig. 42.2). The lesions have the potential for scarring and dyspigmentation, typically with hypopigmentation in the center and hyperpigmentation at the periphery, but sometimes with vitiligo-like depigmentation [2, 35–46]. Prevalence of photosensitivity in children with DLE is thought by some authors to be lower than in adults [46]. However, Mokhtar et al. [52] and

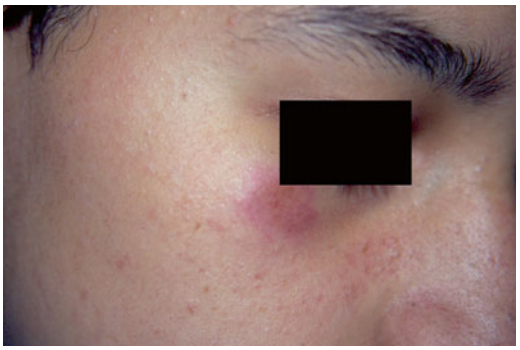

Fig. 42.3 LE tumidus—erythematous, indurated, urticarial plaque with no scale or follicular plugging

Cherif et al. [40] in two Tunisian studies reported a prevalence of photosensitivity as high as 81 %.

Several authors have described linear chronic DLE as a rare manifestation of lupus in which the erythematous, atrophic, dyschromic lesions are located along the lines of Blaschko, affecting more commonly the face and neck. Unlike typical DLE, the linear variant onset occurs frequently in childhood [53–56].

Lupus Tumidus

LE tumidus represents an uncommon but distinct subtype of CCLE. The lesions are characterized by erythematous, indurated, urticarial, nonscarring plaques in sun-exposed areas. Unlike other variants of CCLE, there is no epidermal involvement; therefore they lack associated scale or follicular plugging (Fig. 42.3). The lesions tend to resolve without scarring or atrophy [50, 57].

Lupus Panniculitis/Lupus Profundus

Intense inflammation in the subcutaneous tissue leads to indurated plaques, which may have overlying hyperpigmentation in patients of color, that can evolve to depressed, disfiguring areas. The lesions of lupus panniculitis occur predominantly on the face, upper arms, upper trunk, breasts, buttocks, and thighs (Fig. 42.4). Some patients have discoid lesions overlying the panniculitis and it is sometimes referred to as lupus profundus [40, 42, 58].

Chilblain Lupus Erythematosus

Chilblain lupus erythematosus (CHLE) is a rare, chronic form of CLE. It consists of red or dusky purple papules and plaques on the toes, fingers, and sometimes the nose, elbows, knees, and lower legs (Fig. 42.5). The lesions are triggered or exacerbated by cold, particularly in moist cold climates [59, 60].

Pathogenesis

- **SCLE is associated with anti-Ro antibodies**

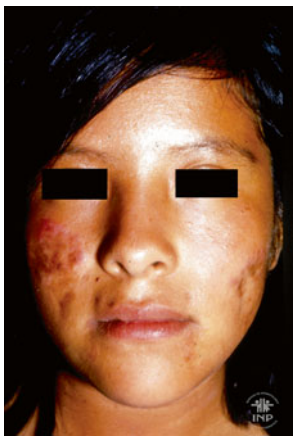

Fig. 42.4 Lupus profundus—deep infiltration with overlying discoid lesions and residual atrophy on the face of a teenager

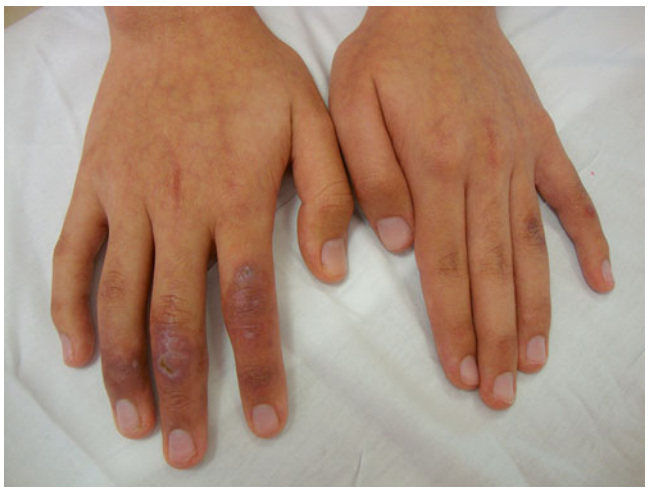

Fig. 42.5 Dusky purple plaques on the fingers of a teenager with chilblain lupus

- **Familial CHLE is associated with missense mutations in TREX1**
- **The sequence of events from the initiation of the autoimmune response to development of lesions is largely unknown**

Regarding the pathogenesis of lupus-specific skin lesions, the full sequence of events leading from initiation of the autoimmune response to the development of skin lesions is not known. In DLE, LE tumidus, and lupus panniculitis, there is no clear-cut association of a specific autoantibody with a particular skin lesion. There is an association of antibodies to double-stranded DNA with acute cutaneous lupus and of antibodies to Ro with subacute cutaneous lupus. Lee et al. have also found autoantibodies to Ro in the majority of patients with chronic cutaneous lupus, raising the possibility that the immune response to Ro, whether primary cell mediated or autoantibody mediated, may be important in CCLE [61, 62].

Sporadic and familial (autosomal dominant-inherited) CHLE have been reported [63]. In familial CHLE, two missense mutations in TREX1 encoding the 3′–5′ repair exonuclease 1 were described in affected individuals. The pathogenesis of sporadic CHLE remains unknown [63, 64].

Diagnosis and Differential Diagnoses

- **Diagnosis depends on clinical features in the infant and the demonstration of NLE-associated antibodies on maternal serum**
- **Skin biopsy is useful when the diagnosis is in doubt**
- **Several differential diagnoses include seborrheic dermatitis, atopic dermatitis, tinea corporis, among others**

The diagnosis of SCLE and CCLE is usually established based on the clinical features. It may be aided by skin biopsy and laboratory parameters.

Subacute Cutaneous Lupus Erythematosus

SCLE has a distinct histopathology with epidermal atrophy, hydropic degeneration of basal cell layer, and a dermal lymphohistiocytic infiltrate. The infiltrate is typically located in the upper dermis in an interface and perivascular pattern, and it is sparse in comparison to DLE lesions. Compared to DLE where over 90 % of patients have immunoreactants at the dermoepidermal junction, 40–50 % of SCLE patients do not show immune deposits [65].

It is important to clinically differentiate SCLE from other eruptions more common to children, such as atopic dermatitis, urticarial drug eruptions, and psoriasis vulgaris, because progression to SLE may occur [28].

Chronic Cutaneous Lupus Erythematosus

In DLE lesions, disease activity involves the epidermis, upper and lower dermis, and hair follicles. There is hyperkeratosis, follicular plugging, and keratinocyte damage in the epidermis. Colloid bodies may be prominent in the epidermis and upper dermis. There is hydropic degeneration of the basal cell layer and dermal-epidermal and follicular basement membrane zones are visibly thickened (more apparent in PAS-stained sections). The dermal lymphohistiocytic infiltrate is often pronounced, affecting both upper and lower dermis in interface, perivascular and periadnexal locations. Edema, vasodilation, and mucin deposits may be present in the dermis. According to George et al., vacuolization of the basal cell layer and perivascular and periadnexal lymphocytic infiltrate have an important diagnostic significance in childhood, whereas epidermal lesions can be absent [66]. Direct immunofluorescence (DIF) in lesional skin is not specific, and its absence does not eliminate the diagnosis of DLE. DIF can be helpful in establishing the diagnosis of DLE; in 80 % of the cases, granular deposits of IgG, IgM, or complement are present along the basal membrane zone (BMZ) [66]. In rare instances, laboratory tests show inflammation associated with low titers of antinuclear antibodies.

DLE early lesions may have not developed some characteristic features and appear erythematous and intensely inflamed and can be confused with Jessner's lymphocytic infiltrate, polymorphous light eruption, lymphocytoma cutis, lymphoma cutis, granuloma faciale, and sarcoidosis. Scalp and oral lesions may need to be distinguished from lichen planus.

In *lupus tumidus* epidermal findings tend to be sparse or absent. The major findings are a pronounced lymphohistiocytic dermal infiltrate and marked mucin deposits [57].

Lupus tumidus lesions are similar in appearance to those of Jessner's lymphocytic infiltrate. Polymorphous light eruption may clinically simulate lupus tumidus, but histologically the two can be distinguished.

In *lupus panniculitis*, the major histologic findings are in the subcutaneous tissue, with a predominantly lobular lymphohistiocytic panniculitis. The infiltrate may be also found in the lower dermis, and in some cases, there is also an overlying discoid lesion.

In *chilblain lupus*, histologic findings include a deep inflammatory infiltrate with perivascular distribution and granular deposits of immunoglobulins and complement along the basement membrane. Some affected individuals show antinuclear antibodies or immune complex formation, whereas cyroglobulins or cold agglutinins are absent [56].

Treatment

- **Strict photoprotection and topical corticosteroids**
- **Hydroxychloroquine for nonresponding limited CCLE and for disseminated lesions**
- **Calcineurin inhibitors, dapsone, and thalidomide used in some cases**

The aim should be to treat lesions of DLE at an early stage to prevent scarring. This is more so if scalp is involved, as the sequela is scarring alopecia which may cause negative psychological impact upon the affected child.

For localized lesions, mid-potency topical or intralesional corticosteroid is the first line of treatment along with strict photoprotection. In limited skin lesions not responding to topical therapy, oral hydroxychloroquine (4–6 mg/kg/day) should be started. In disseminated skin lesions, systemic treatment is compulsory. These include hydroxychloroquine (4–6 mg/kg/day) and/or oral corticosteroid (1–2 mg/kg/day). In severe cases, intravenous methylprednisolone pulse therapy may be given. Children on hydroxychloroquine therapy need baseline and thereafter routine ophthalmic evaluation [21].

Other therapeutic modalities for childhood DLE are calcineurin inhibitors (pimecrolimus 1 % cream, tacrolimus 0.03 and 0.1 % ointment), dapsone, and thalidomide.

Dapsone (50 mg/day) is a well-tolerated drug used in childhood DLE [30]. Cherif et al. [40] used dapsone for 8 months in a child with complete remission. Moises-Alfaro et al. [41] used thalidomide alone or in combination with chloroquine in eight patients. Children with DLE on systemic therapy need clinical evaluation every 4–6 months along with repetition of laboratory parameters every 6 months.

Prognosis

Subacute Cutaneous Lupus Erythematosus

Until more published experience with childhood-onset SCLE is available, discussion of prognosis and risk should be very guarded.

Chronic Cutaneous Lupus Erythematosus

Progression to SLE is probably more frequent in children than in adults. George and Tunnessen reported a progression of DLE to SLE in 5 of the 16 children included in their study [46]. More recently, Moises-Alfaro et al. estimate the risk of SLE in children with DLE to be as high as 26 % over a 3-year follow-up period [41]. These authors also contend that the confined or disseminated character of the lesions, the early onset of the disease (age less than 10 years), duration, the presence of antinuclear antibodies, and poor response to antimalarials are not predictive factors for progression to SLE [41]. On the other hand, inflammatory arthritis may herald progression to SLE [41].

Regarding chilblain lupus up to 20 % of patients develop SLE [64].

Ongoing Research

CLE pathogenesis currently remains unclear and is likely multifactorial. It has been recently demonstrated that patients with SCLE and DLE, but not lupus tumidus, may share an underlying defect in IFN signaling with SLE. Apparently, the level of gene expression correlates with cutaneous disease activity. Since these findings support a shared pathogenesis between SLE and some subtypes of CLE, research is following that line of evidence [67, 68].

Conclusion

CLE may present with acute, subacute, and chronic lesions. SCLE is extremely rare in childhood and CCLE presents seldom in pediatric patients. The diagnosis of CLE is clinical, but may be aided by skin biopsy. Treatment mainly consists of strict photoprotection and mid-potency topical corticosteroids. Follow-up is mandatory since all forms of CLE may progress to SLE.

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Autoinflammatory Syndromes

43

Antonio Torrelo and Lucero Noguera

Abstract

Autoinflammatory syndromes are characterized by recurrent attacks of fever and systemic inflammation over a baseline of continuous low-grade hyperfunctioning of the innate immune system. Four main groups, namely the hereditary recurrent fevers, the pyogenic/pustular disorders, the granulomatous disorders and the proteasome-related syndromes are of interest to the dermatologist. Varied genetic mechanisms give rise to these intriguing phenotypes, which can be in many cases specifically targeted with biologic therapy that restores normality and permits a normal development of the affected children.

Keywords

Cryopyrin • Inflammasomes • Interleukin-1 • Proteasome

Introduction

The so-called autoinflammatory syndromes (AISs) are a group of rare diseases that occur due to mutations in genes codifying proteins with a role in inflammation pathways of the innate immune system [1]. They are characterized by recurrent fevers and systemic inflammation appearing early in life and are genetically transmitted in most cases. There are several classifications of AISs in relation to the genetic background (Table 43.1), but a useful classification for the dermatologist will be followed according to the main clinical manifestations of the syndrome (Table 43.2).

Hereditary Recurrent Fevers (Urticarial and Vasculitic Fevers)

- **Urticarial and erythematous eruptions are the cutaneous hallmark of the hereditary recurrent fevers**
- **Cold-induced urticaria in the newborn is very suspicious of hereditary recurrent fevers**
- **Amyloidosis may be an end-stage complication**

This group encompasses AISs coursing with recurrent fevers and erythema. They present clinically with recurrent episodes of fever and erythematous swellings that can range from discrete urticarial wheals to large erythematous macules; the lesions can occur daily or at variable intervals from days to weeks. Several clinical manifestations of systemic inflammation accompany the eruption.

Familial Mediterranean Fever

- **Familial Mediterranean fever (FMF) is due to mutations in the *MEFV* gene, codifying pyrin or marenostrin**
- **Erysipeloid plaques are the most characteristic cutaneous lesions**
- **Colchicine may control the disease**

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Table 43.1 Autoinflammatory diseases with dermatologic manifestations

- Periodic fever syndromes (PFS):
  - Familial Mediterranean fever (FMF)
  - Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
  - Hyperimmunoglobulinemia D syndrome (HIDS)
  - Periodic fever with aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA)
- Cryopyrin-associated periodic syndromes (CAPS):
  - Familial cold autoinflammatory syndrome (FCAS)
  - Muckle–Wells syndrome (MWS)
  - Neonatal onset multisystemic inflammatory disorder (NOMID)
- CAPS related syndromes:
  - Deficiency of the interleukin-1-receptor antagonist syndrome (DIRA)
  - Deficiency of interleukin 36-receptor antagonist syndrome (DITRA)
- Other autoinflammatory syndromes:
  - Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)
  - NOD2-Associated pediatric granulomatous arthritis (PGA):Blau syndrome/early
  - Onset sarcoidosis
  - Majeed syndrome
  - Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome
  - Beçet syndrome
  - Schnizltler syndrome
  - Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome
  - Chronic recurrent multifocal osteomyelitis (CRMO) sporadic form
  - Systemic juvenile idiopathic arthritis (Still disease) and adult onset
  - Pyoderma gangrenosum, acne and suppurative hidradenitis (PASH)
  - Possible autoinflammatory diseases:
    - Inflammatory bowel disease
    - Sweet syndrome, pyoderma gangrenosum and other neutrophilic dermatoses

Table 43.2 Classification of autoinflammatory diseases with dermatologic cutaneous findings

Disease	Defective gene
Hereditary recurrent fevers	
Familial Mediterranean fever	*Pyrin (marenostrin)*
Mevalonate kinase deficiency (hyper IgD) syndrome	*Mevalonate kinase (MVK)*
TNF receptor-associated periodic syndrome (TRAPS)	*TNFRSF1A*
Cryopyrin associated periodic syndromes (CAPS)	
CINCA/NOMID syndrome	*NLRP3*
Muckle–Wells syndrome	*NLRP3*
Familial cold autoinflammatory syndrome (FACS)	*NLRP3*
NLRP12-associated periodic fever (NAPS)	*NLRP12*
Pyogenic diseases	
Deficiency of IL-1 receptor antagonist (DIRA)	*IL1RN*
Deficiency of IL-36 receptor antagonist (DITRA)	*IL36RN*
Pyogenic arthritis, pyoderma, acne (PAPA) syndrome	*PSTPIP1*
Majeed syndrome	*LPIN2*
Granulomatous and histiocytic diseases	
Blau syndrome	*NOD2 (CARD15)*
H syndrome	*SCL29A3*
Proteasome instability syndromes	
CANDLE syndrome	*PSMB8, others*
JMP syndrome	*PSMB8*
Nakajo–Nishimura syndrome	*PSMB8*
Others	
Pityriasis rubra pilaris	*CARD14*
Disseminated superficial actinic porokeratosis	*MVK*
Autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation	*PLCG2 (Phospholipase C, gamma 2)*

FMF is the paradigm of the periodic fever syndromes. It is an autosomal recessive (AR) disorder due to mutations in the gene *MEFV* (MEditerranean FeVer), which encodes a protein named pyrin or marenostrin [2, 3]. Pyrin is a main regulatory component of the NLRP3 inflammasome, a large protein complex that takes part in inflammation signaling pathways such as the IL-1β pathway [4].

Clinical Manifestations

FMF patients present episodic attacks of fever that typically last less than 72 h, abdominal pain, pleurisy, mono or oligoarticular arthritis, and/or arthralgias [5]. Attacks are self-limited and between them the patient remains asymptomatic. The interval between attacks is variable. Exercise, emotional stress, exposure to extreme temperatures, and hormonal changes can trigger the attacks [5]. Amyloidosis is a severe complication that could appear in untreated patients. Erysipeloid-like lesions, which appear in 15–20 % of children, are the characteristic cutaneous manifestation of FMF [6–8]. They usually appear in the lower extremities as well-circumscribed edematous and erythematous plaques. Histopathology shows a predominantly neutrophilic infiltrate with nuclear dust [9]. Purpuric lesions on the face, trunk, and extremities have also been reported in children.

Treatment

Colchicine is the treatment of choice; it reduces the frequency, intensity, and the duration of the attacks [10]. In patients who do not respond to colchicine, it is important to verify the compliance with therapy. Intravenous colchicine could be tried as some of these not-responders do respond to this regime. There are isolated reported cases of truly colchicine-resistant patients that responded to thalidomide, to anti-TNFα agents such as etanercept and infliximab, and to the recombinant IL-1 receptor antagonist anakinra [11, 12].

Cryopyrin-Associated Periodic Syndromes

Cryopyrin-associated periodic syndromes (CAPS), also called cryopyrinopathies, are a group of three overlapping autosomal dominant syndromes, which are due to self-activating mutations in the *NLRP3* gene (also called CIAS1). NLRP3 product is the protein called cryopyrin, which is part of a multiprotein inflammasome complex (the NLRP3 inflammasome), which in response to certain stimuli activates the caspase 1 cascade that leads to production of pro-inflammatory cytokines, mainly IL-1β and IL-18 [13].

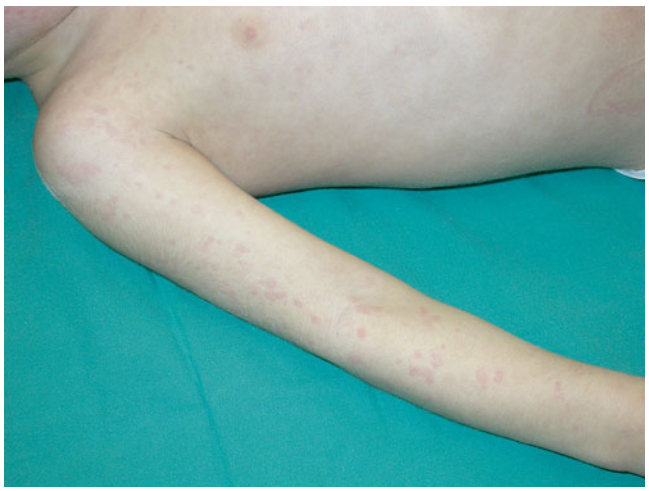

Fig. 43.1 Urticarial rash in NOMID syndrome

Clinical Manifestations

- **Neonatal urticaria is the earliest sign of the disease**
- **Peculiar cherubic face is seen**
- **Arthropathy and CNS are often involved**

CAPS include familial cold autoinflammatory syndrome (FCAS, or familial cold urticaria), Muckle–Wells syndrome (MWS, urticaria-deafness-amyloidosis syndrome), and neonatal onset multisystemic inflammatory disorder (NOMID, also named as chronic infantile neurological cutaneous and articular (CINCA) syndrome). NOMID is the most severe form of CAPS. Symptoms appear shortly after birth, usually before 6 months of age. The triad of fevers, skin urticarial rash, severe arthropathy, and central nervous system disorders characterizes NOMID [14, 15] (Fig. 43.1). Patients with NOMID show abnormal facial features, including flattening of the nasal bridge, macrocephaly, frontal bossing, and protruding eyes [16]. Neurological manifestations develop with time, and include chronic aseptic meningitis, cerebral atrophy, sensorineural hearing loss, and developmental delay. Eye manifestations, such as anterior uveitis, papilledema, or blindness, also occur in NOMID [17]. About 50 % of patients have severe arthropathy before 12 months of age. Secondary amyloidosis may appear due to chronic inflammation [1]. An erythematous skin eruption resembling urticaria is usually present in the neonatal period or may appear before 6 months of age. The rash persists during the whole life of patients. On histopathology, superficial and deep perivascular infiltrates are seen composed mainly of neutrophils, lymphocytes, and some eosinophils [18].

Treatment

Anakinra, the IL-1 receptor antagonist, has shown dramatic improvement of CAPS, although not all patients respond equally [19]. Rilonacept and canakinumab can achieve complete and sustained responses in almost all cases of CAPS [19].

Pyogenic Disorders

- **Pustules on an erythematous basis in a newborn with fevers are the main presentation**
- **Osteoarticular symptoms are frequent**
- **Histopathology resembles pustular psoriasis in many cases**

The deficiencies of the interleukin-1-receptor antagonist syndrome (DIRA) and of interleukin-36-receptor antagonist syndrome (DITRA) are the paradigm of pustular eruptions associated with periodic fever. Other diseases in this group include pyogenic arthritis, pyoderma, acne (PAPA) syndrome, and Majeed syndrome. In all of them, the main cutaneous lesions are pustular eruptions, which show marked neutrophil infiltration with prominent intraepidermal neutrophil accumulations.

DIRA shares etiopathogenic features with CAPS but clinical manifestations differ from them. The deficiency of interleukin-1-receptor is secondary to homozygous mutations in IL1RN [20–23]. The lack of antagonistic activity of IL-1 receptor leads to a continuous activation of inflammatory pathways through IL-1. Patients with DIRA present chronic recurrent episodes of aseptic osteomyelitis and periostitis and periarticular swelling shortly after birth [24]. Fever and failure to thrive are common problems in DIRA. Respiratory distress, pulmonary infiltrates, and thrombotic episodes may also occur [20, 21, 25]. In the skin, generalized erythematous plaques with pustules resembling pustular psoriasis appear at birth or very early in infancy [20, 21, 25]. Skin biopsies show epidermal parakeratosis with subcorneal spongiform neutrophilic pustules and heavy dermal neutrophilic infiltrates [20–25]. Daily subcutaneous injections with anakinra, the recombinant analogue of IL1RN, often lead to complete clinical resolution of manifestations in most patients [20–25].

Mutations in the IL-36 receptor antagonist (IL-36RN) have been identified as the cause of some familial and sporadic cases of generalized pustular psoriasis (GPP) [26, 27]. IL-36RN is a protein of the IL-1 cytokine family, which has an inhibitory role in inflammatory pathways such as the NF-κB [26, 28]. DITRA appears as recurrent episodes of skin eruption along with fever, malaise, and asthenia without involvement of other organs. The episodes usually begin during the childhood but some adult onset cases were reported as well. Some triggers such as bacterial and viral infections, menstruation, pregnancy, or drugs have been reported [26, 27]. Histology of the skin lesions show features of pustular psoriasis, including spongiform pustules, psoriasiform acanthosis, and parakeratosis in the stratum corneum [27]. Anakinra has been reported effective in a few cases of DITRA, but the disease is usually refractory to all treatments tried [28].

Granulomatous and Histiocytic Disorders

- **Blau syndrome shows diffuse erythematous papules.**
- **Histopathology shows features very close to sarcoidosis.**
- **Arthritis and uveitis are common manifestations of Blau syndrome.**

The NOD2-associated pediatric granulomatous arthritis (PGA) or Blau syndrome/early-onset sarcoidosis is the paradigm of granulomatous AIS. Hyperfunctioning mutations in the *NOD2* gene (also known as CARD15) are behind the pathophysiology of all these entities [29–31]. Missense mutations resulting in constitutive self-activation of NOD2 lead to increased basal NFκB activation [32]. The classical manifestations of Blau syndrome are polyarticular synovitis, granulomatous acute anterior uveitis and skin rash [33]. All of them start early in life, mostly before 4 years of age. Other less common manifestations of Blau syndrome are nonperiodic fever, granulomatous lymphadenopathy, hepatosplenomegaly, granulomatous infiltration of salivary glands, pneumonitis, glomerulonephritis, and cranial neuropathy [34]. The skin lesions are usually observed in early childhood and consist in asymptomatic, reddish, lichenoid papules that may be localized or generalized in trunk and extremities sparing the palms and soles (Fig. 43.2). On the face, they may show a 'butterfly' distribution. Histological examinations show noncaseat-

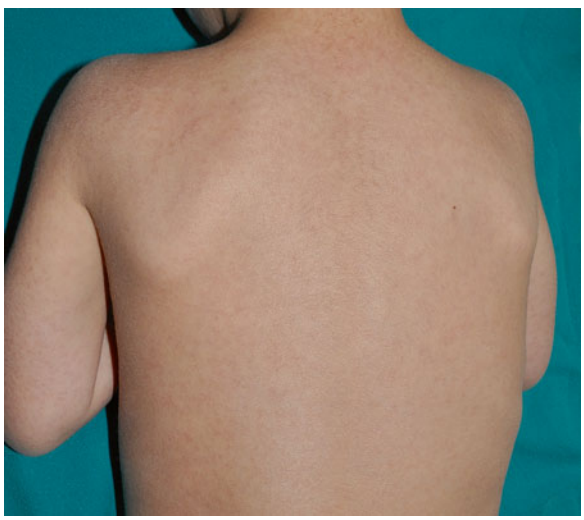

Fig. 43.2 Diffuse papules in Blau syndrome

ing granulomas in dermis with epithelioid and multinucleated giant cells, which are thus indistinguishable from sarcoidosis [33, 34]. A panniculitis resembling erythema nodosum and ichthyosiform scaling have also been reported. Cutaneous lesions may respond to chronic therapy with erythromycin; corticosteroids, methotrexate, and anti-TNF drugs can be necessary for extracutaneous manifestations. Thalidomide has been reported to show good efficacy in this disorder. There are occasional reports of the response with the use of anakinra [35].

Proteasome Instability Disorders

- **Recurrent purpuric plaques and recurrent attacks of fever characterize CANDLE syndrome**
- **Histopathology shows mononuclear infiltrates with bizarre nuclei**
- **Lipodystrophy and delayed growth are prominent features**

A group of allelic diseases characterized by autoinflammation and lipodystrophy are known to be due to mutations in the β5i subunit of the immunoproteasome, coded by the gene *PSMB8*. They include the chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, the "JMP" syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy) and a similar phenotype named the Nakajo–Nishimura syndrome in Japan [36, 37].

Daily or recurrent episodes of fever since early infancy are characteristic of CANDLE syndrome. Recurrent annular erythematous or purpuric edematous plaques with raised borders are seen in all patients with CANDLE syndrome (Fig. 43.3). They appear predominantly on the trunk but also on the face and limbs, especially over the interphalangeal joints. When they resolve they leave hyperpigmented or ecchymotic lesions. New lesions coincide with older ones all along the evolution. A characteristic violaceous edema of the eyelids and lips develops in childhood. Low weight and height and a progressive loss of fatty tissue are prominent since early childhood. Hepatomegaly, splenomegaly, arthralgia without arthritis, and a myriad of multiorgan inflammatory attacks are characteristic, which may be severe or even fatal. Laboratory analyses showed chronic anemia and mild elevation of liver enzymes [36]. Histological examination of skin lesions is very distinctive and shows a striking dense dermal perivascular and interstitial infiltrates sometimes with subcutaneous involvement, composed of mononuclear cells with myeloid appearance with atypical features. Neutrophils and eosinophils may also be present [36]. Immunohistochemistry demonstrates that the infiltrate is mainly composed of both macrophage and myeloid cells.

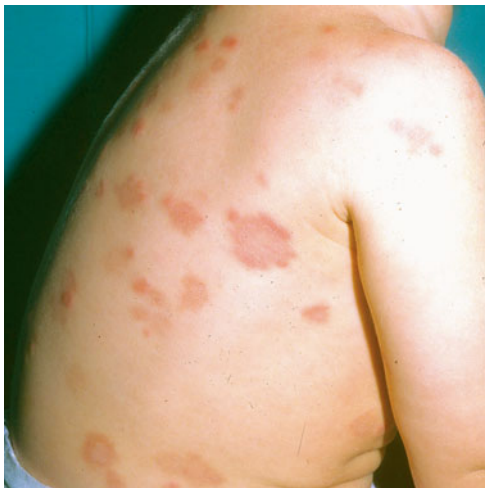

Fig. 43.3 Purpuric plaques in CANDLE syndrome

Treatment

NSAIDs, oral corticosteroids, and methotrexate are minimally effective in controlling the symptoms. Colchicine, dapsone, cyclosporine, immunoglobulin infusions, and anti-TNFα drugs have shown no improvement. No other therapy has been successful so far [36].

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Acute Hemorrhagic Edema

44

Antonio Torrelo and Lucero Noguera

Abstract

Acute hemorrhagic edema (AHE) is a peculiar form of small-vessel vasculitis affecting mainly children below the age of 2. Purpura with a cockade or targetoid appearance, along with mild limb edema, are the main clinical manifestations. Children affected with AHE usually show a good general status and need no treatment. Complications are uncommon.

Keywords

Purpura • Vasculitis

Introduction and Epidemiology

- **Acute hemorrhagic edema (AHE) occurs mainly in infants and is rare in children over 2 years**
- **AHE not only shares many features with Henoch–Schönlein purpura but also has distinct manifestations**
- **Immune-complex-mediated vasculitis is the substrate of AHE**

The term AHE denotes a form of acute and self-resolving leukocytoclastic vasculitis that usually affects children below the age of 2 [1–4]. Some authors consider AHE as the counterpart of Henoch–Schönlein purpura in infants, but there are several important differential features that allow considering AHE as a distinct entity. As with other forms of cutaneous vasculitis, AHE is due to deposition of immune complexes in the vessel walls, leading to necrotizing vasculitis. Upper respiratory infections, drugs, and vaccinations can precede AHE, and a role for bacteria or viruses has also been suspected.

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Clinical Presentation

- **Patients usually show a good general status**
- **The main skin manifestation is targetoid purpura on the limbs**
- **Edema of distal areas is common**

The skin eruption is characteristic enough to permit a diagnosis at first glance in most cases [5]. The term purpura 'en cockades' has been classically used as a description and is very representative of the disease. After an initial phase of urticarial papules and plaques, purpuric macules appear and expand centrifugally, leaving darker centers with surrounding rings of purpura, thus providing a cockade or targetoid appearance (Figs. 44.1 and 44.2). Confluence of lesions may yield large polycyclic macules. These characteristic lesions have a centrifugal distribution, with a striking involvement of the ears, cheeks, and upper and lower limbs, whereas the trunk is usually not involved. The oral mucosa may rarely be affected by petechiae. Less commonly, atypical manifestations such as necrotic or bullous lesions can occur [6]. Edema of the ears, face, wrists, hands, ankles, and feet is a common feature that accompanies the skin lesions (Fig. 44.3). Fever may also exist, but many cases only show minimal increases in body temperature. Besides the striking skin lesions, the patients do not show any other associated symptoms or complications and remain in good general status throughout the disease.

Laboratory analyses are usually inconspicuous. Leukocytosis, thrombocytosis, and elevated ESR may be

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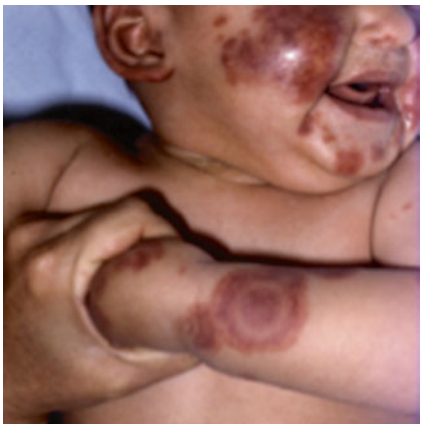

Fig. 44.1 Targetoid purpura on face and forearms (courtesy Dr. Carola Durán)

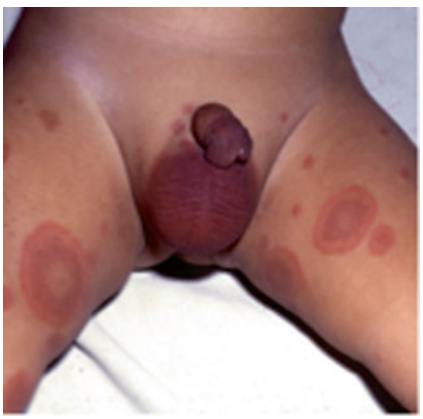

Fig. 44.2 Targetoid purpura on thighs (courtesy Dr. Carola Durán)

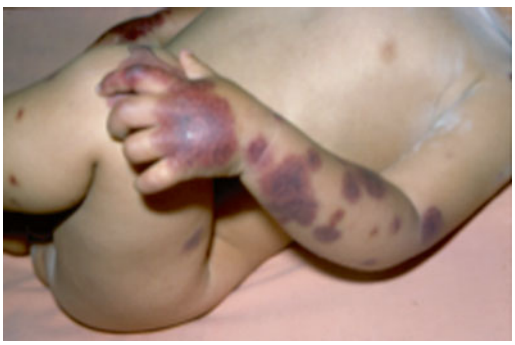

Fig. 44.3 Distal edema and purpura on hands and forearms (courtesy Dr. Carola Durán)

present. There are usually no signs of urinary or gastrointestinal bleeding. Occasionally, circulating immune complexes can be found [7]. On histopathology, skin biopsies show leukocytoclastic vasculitis in the small vessels of the dermis. A deposition of C3, fibrinogen, and immunoglobulins (including IgM, IgG, and IgA) have been noted in one-third of the cases [7, 8].

Treatment

- **No treatment is needed**
- **Complications are very unusual**
- **The eruption resolves spontaneously in a few weeks**

The skin eruption of AHE usually resolves spontaneously in less than 3 weeks, although exacerbations and recurrences have been reported [9]. No specific treatment is recommended, and corticosteroids may even lead to complications and are thus not indicated. Complications are very unusual, but children with AHE should be controlled because AHE may clinically overlap with Henoch–Schönlein purpura, and this diagnosis should not be overlooked. Anecdotal reports exist of intestinal intussusception [10, 11] and liver involvement [12] in AHE.

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Henoch–Schönlein Purpura

45

Antonio Torrelo and Lucero Noguera

Abstract

Henoch–Schönlein purpura (HSP) is the most common type of vasculitis in children. It usually presents as an acute onset of palpable purpura, mainly located on the lower extremities. Systemic involvement is very frequent, and complications may occur. An accurate diagnosis with skin biopsy showing leukocytoclastic vasculitis and IgA deposits is much recommended. Most cases will be managed conservatively with rest and oral NSAIDs.

Keywords

Palpable purpura • IgA • Leukocytoclastic vasculitis

Introduction

Henoch–Schönlein purpura (HSP) is the most common type of small vessel vasculitis in children. In fact, most cases of HSP do occur in children over 4 years and has been rarely reported in infants [1, 2]. HSP is due to the deposition of IgA immune complexes in the small vessel walls, leading to necrotizing vasculitis. Infectious agents, vaccinations, and drugs have been claimed as triggers for HSP. Vasculitis may affect the skin, joints, gastrointestinal (GI) tract, kidney, and less commonly other organs.

Clinical Features

- **Usually appears as acute onset of palpable purpura in the lower extremities.**
- **Abdominal and joint manifestations are common; kidney involvement is common and may occur later in the disease.**
- **Leukocytoclastic vasculitis with IgA deposition is demonstrated on skin biopsies.**

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The onset of HSP is usually acute with simultaneous involvement of the skin and other organs. A more gradual onset is also possible. The skin lesions are present in most cases and are the presentation sign in up to 75 % of patients [1, 2]. Initially, urticarial lesions or small macules or papules may appear, but rapidly the palpable purpura turns the main skin sign of HSP. Small purpuric papules are symmetrically distributed on ankles, legs, and less commonly on thighs and buttocks (Fig. 45.1). The face, trunk, or arms may rarely be involved, but HSP seldom affects mucosae, palms, and soles. Typically, a small, pinpoint purpuric papule is surrounded by a purpuric macule that may show papules in its periphery, giving the appearance of a rosette; however, this typical appearance is not always seen (Fig. 45.2). In dark-skinned children, purpura may be difficult to recognize in the early stages. If vascular damage is severe, larger ecchymosis, blisters, and necrotic lesions may occur. Lesions may be more pronounced or appear at sites of trauma. There may be painful edema of the scalp, face, periocular region, ears, limbs, and scrotum, especially in younger children, then resembling acute hemorrhagic edema. Usually, typical skin lesions heal in 2 or 3 weeks, but exacerbations can occur lasting even weeks or months.

Systemic involvement is usually present. A self-limited arthritis of the knees and ankles can be seen in 60–80 % of cases and can be the presenting sign in up to 25 % of patients [1, 2]. Abdominal pain with fecal occult blood is the most characteristic gastrointestinal complaint, although more

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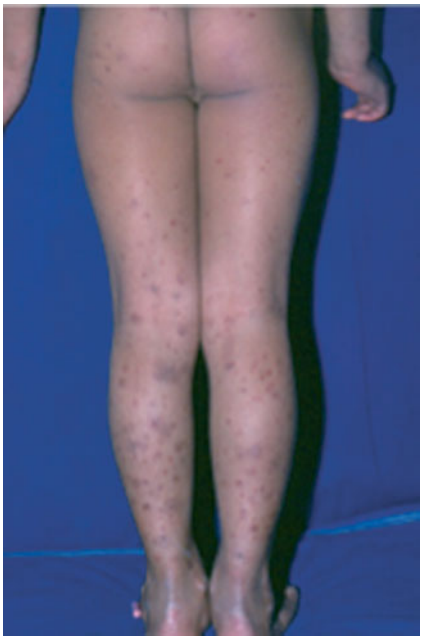

Fig. 45.1 Palpable purpura on the lower limbs in a girl with HSP (courtesy Dr. Carola Durán)

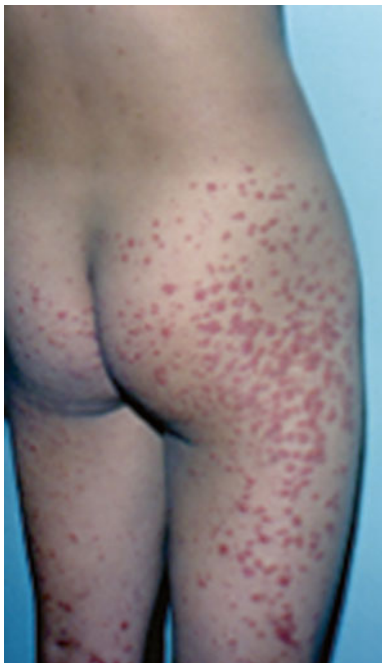

Fig. 45.2 Purpuric papules on the thighs and buttocks in HSP (courtesy Dr. Carola Durán)

profuse GI bleeding may occur; other GI complications include intestinal perforation and intussusception [2, 3]. Kidneys may be affected in up to 60 % of cases [2], usually a delayed manifestation. Microscopic hematuria and proteinuria may evolve into nephrotic syndrome, acute nephritis, and rarely acute renal failure. Prognostic factors associated with kidney involvement include abdominal pain, decreased activity of factor XIII, and persistence of purpura for more than 1 month [3, 4]. Varied neurological symptoms such as headache, irritability, or seizures may indicate CNS involvement.

Laboratory analyses may show anemia, leukocytosis, and increased ESR; serum chemistry may reveal kidney or GI involvement. Urinalysis is mandatory to rule out hematuria and proteinuria. Coagulation studies are normal. Sometimes, elevated levels of IgA, IgA circulating immune complexes, IgA rheumatoid factor, and IgA antineutrophil cytoplasmic antibodies can be observed [3, 4]. Skin biopsy is recommended from recently appeared lesions and shows small vessel leukocytoclastic vasculitis. Late lesions may fail to reveal necrotizing vasculitis. Direct immunofluorescence (DIF) of very recent lesions demonstrates perivascular deposits of IgA, C3, and fibrinogen; such deposits may be lost after 48 h.

Differential Diagnosis

Other forms of small vessel vasculitis may mimic HSP. The IgA deposits (DIF) will differentiate HSP from other types of leukocytoclastic vasculitis. Diagnostic criteria have been developed, but their use has been debated [5]. Lupus erythematosus, Wegener disease, or cryoglobulinemia may also be considered in the differential. As stated earlier, acute hemorrhagic edema can be considered within the spectrum of HSP.

Treatment

- **Systemic involvement will lead the therapeutic choices, especially kidney disease.**
- **Most cases only need rest and oral NSAIDs.**
- **The use of systemic corticosteroids is debatable.**

Kidney involvement is the most important prognostic factor and may occur later in course of the disease, thus requiring monitoring for some months after the skin lesions have healed [6]. If there is no renal involvement, the treatment of HSP should include rest and oral NSAIDs for joint pain. The use of systemic steroids is debatable. They have been used extensively in cases of abdominal or joint involvement, but their role in preventing renal involvement is questioned [7, 8]. Renal disease should be managed by a nephrologist.

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Kawasaki Disease

46

Lucero Noguera and Antonio Torrelo

Abstract

Kawasaki disease (KD) is a systemic vasculitis mainly affecting children below 5 years of age. Diagnosis is made upon a combination of criteria, including persistent fever; edema, erythema, or desquamation of the extremities; polymorphous exanthema; conjunctival injection; erythema of the lips and oral mucosa; and lymphadenopathies. Many cases do not meet all diagnostic criteria but should also be considered for therapy. IVIG and aspirin are the main therapeutic measures.

Keywords

Vasculitis • Coronary aneurism • Perineal rash • Superantigens

Introduction

Kawasaki disease (KD) is a systemic vasculitis primarily affecting children. It was first described by Tomisaku Kawasaki in 1967 [1], and until today its etiology remains unknown. Diagnosis of the disease is made on clinical grounds, and KD can lead to systemic complications, including heart disease in up to 25 % of the patients [2]. KD is now considered the most common cause of acquired heart disease in children in developed countries worldwide [3].

Epidemiology

- **Most cases occur below the age of 5**
- **Higher prevalence in Asians**
- **Seasonal clustering in winter**

Most cases of KD occur in children under 5 years, although there have been some adult case reports [4]. Male:female ratio is 1.5:1. There is a clear seasonal relation, with exceedingly more cases diagnosed in winter and early spring [3].

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KD has a high prevalence among the Japanese population, with an incidence of 210 cases/100,000 children. Likewise, a high prevalence in Asian descendants and Pacific islander children, especially Japanese descendants living in Hawaii, has been confirmed in epidemiologic studies [5]. There are no data about its incidence or disease burden, morbidity, or mortality among Latin American children. Under reporting of cases is likely in these countries; for that reason, a research network on KD in children from Latin America was recently created [6].

Incidence among the Caucasian population in northern European countries and White non-Hispanic children in the US varies between 5.4–11.7 and 13.7 respectively [5, 7].

Pathogenesis

Although the etiology is unknown, it is widely postulated that KD occurs after an exposure of a genetically susceptible individual to a yet unidentified agent, possibly of infectious nature. A prospective case-control study conducted in Taiwan aiming to investigate possible links between common viral infections and KD found that cases of KD were more likely to have overall positive rates of viral PCR in throat and nasopharyngeal swabs for adenoviruses, enteroviruses, rhinoviruses, and coronaviruses [8]. KD is characterized

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by an endothelial cell injury, which could be due to abnormal cytokine production and to generation of cytotoxic antibodies against the endothelial cells [9]. All data suggest that this activation of the immune system occurs after infection only in genetically predisposed individuals. The most consistently associated genetic variants are nonsynonymous polymorphisms in a high affinity receptor for immunoglobulin G (FCGR2A) and variants in the region of the T-cell regulator ITPKC, a kinase of IP3 (inositol 1,4,5-triphosphate), a second messenger molecule involved in the Ca2+/NFAT (nuclear factor of activated T-cells) pathway, or in caspase-3 (CASP-3), as confirmed in some genome-wide association studies (GWAS) [10].

Clinical Manifestations

- **Persistent fever is the main diagnostic criterion**
- **Cutaneous and mucous manifestations are key for the diagnosis**
- **Many cases of KD do not meet diagnostic criteria**

The diagnosis of KD is made on clinical grounds according to clinical criteria; four out of the five clinical criteria involve the skin or mucous membranes.

The main criterion is fever, which must be present for at least 5 days. Fever must be present and is usually high (>39–40 °C) and resistant to antipyretics. The five clinical criteria include edema, erythema or desquamation of the extremities; polymorphous exanthema; conjunctival injection; erythema of the lips and oral mucosa; and lymphadenopathies (see Table 46.1) [11].

Table 46.1 Kawasaki disease (KD) diagnostic criteria according to the American Heart Association [11]

Epidemiological case definition (classic clinical criteria)[a]
Fever persisting at least 5 days[b]
Presence of at least 4 principal features:
1. Changes in extremities (a) Acute: Erythema of palms, soles; edema of hands, feet (b) Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
2. Polymorphous exanthem
3. Bilateral bulbar conjunctival injection without exudate
4. Changes in lips and oral cavity: Erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
5. Cervical lymphadenopathy (>1.5-cm diameter), usually
Exclusion of other diseases with similar findings

[a]Patients with fever at least 5 days and 4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities detected by 2-D echocardiography or angiography

[b]In presence of 4 principal criteria, KD diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many Kawasaki disease patients may establish diagnosis before day 4

Cutaneous manifestations are striking and should alert the clinician to the possibility of disease; they are present in 90 % of the patients [2]. A maculopapular, nonspecific exanthema may be seen accompanying the fever during the acute phase (Fig. 46.1). It can affect the trunk and sometimes involves more than 90 % of the skin (erythroderma). In other cases, it can be very subtle and affect only the perineal area or the skin folds. The changes in extremities include the erythema and edema, which can be sometimes painful. Desquamation of the tips of the fingers usually occurs later in the disease [12]. Mucous membrane manifestations include nonpurulent, bilateral conjunctivitis and hemorrhagic enanthem, with strawberry tongue with prominent papillae. A bright erythema of the lips with cracks is highly characteristic (Fig. 46.2).

At least one lymph node should be enlarged to more than 1.5 cm in diameter. Enlarged lymph nodes can be conspicuous in some cases. Heart involvement is a major risk and includes in the acute phase the presence of myocarditis or

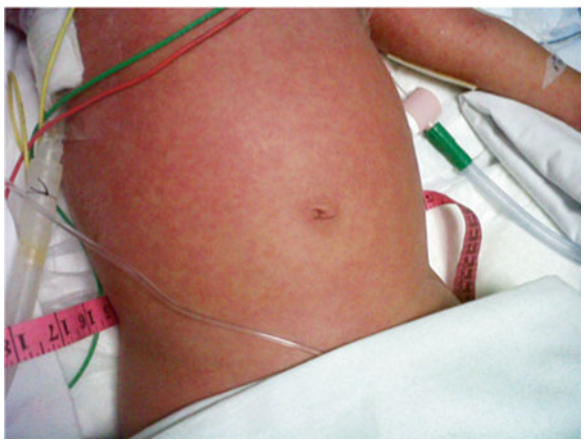

Fig. 46.1 Morbilliform exanthema in Kawasaki disease (KD) (courtesy Dr. Carola Durán)

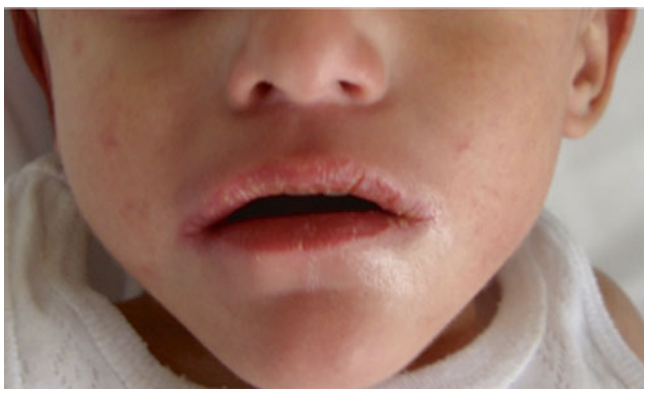

Fig. 46.2 Lip edema and cracking in KD (courtesy Dr. Carola Durán)

Table 46.2 Other clinical and laboratory findings [11]

Cardiovascular findings
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size non-coronary arteries
Raynaud's phenomenon
Peripheral gangrene
Musculoskeletal system
Arthritis, arthralgia
Gastrointestinal tract
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system
Urethritis/meatitis
Other findings
Erythema, induration at Bacille Calmette–Guérin (BCG) inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
Laboratory findings in acute KD
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate (ESR)
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

pericarditis and in later stages the formation of coronary aneurisms. Other clinical findings of KD can be seen in Table 46.2.

The diagnostic criteria of KD have low sensitivity and specificity. Therefore, patients with suspected KD but who do not meet the criteria and whose diagnosis is made upon heart involvement on echocardiography are included under the umbrella term 'incomplete KD' [12].

Complications and Prognosis

KD is a multisystem vasculitis, mainly involving small arteries. Coronary arteries are often affected. It is known that in the acute phase (9–10 days after fever onset) about 30–50 % of children may have a transient coronary dilatation. If left untreated, about 15–25 % of the children will develop coronary artery aneurysms (CAAs), which can lead to myocardial infarction, sudden death, and ischemic heart disease. Myocarditis and pericarditis can also be present in the acute phase, whereas CAAs appear in the convalescence phase. The occurrence of coronary artery lesion (CAL) is associated with many factors in children with KD. Age of less than 1 year or greater than 8 years, male sex, incomplete KD, delayed IVIG treatment after onset, no response to intravenous immunoglobulin treatment, and prolonged fever duration have all been identified as risk factors for the development of CAL [13].

Mortality rates are low (0.01–0.2 %) and peak at 15–45 days after disease onset [14]. There have been some cutaneous and systemic complications in isolated case reports in the literature, including psoriasiform rash after the acute phase, pincer nails, and even Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome following aspirin administration for KD [15, 16]. Up to 2 % of cases may experience recurrence of KD [14].

Treatment

- **Treatment is aimed to prevent heart complications**
- **IV immunoglobulin and aspirin are the first-line treatment of KD**
- **Corticosteroids do not seem to play an important role for treatment**

Treatment of KD is aimed at preventing cardiac complications. Timely IVIG treatment can be delayed by incomplete clinical signs in at least 15–20 % of children with KD. Children with incomplete KD have at least the same risk for CAA than children with KD who meet the diagnostic criteria [17].

Treatment is carried out according to the guidelines of the American Heart Association published in 2004 [11]. The current recommended therapy for KD is the combination of intravenous immunoglobulin (IVIG) 2 g/kg and aspirin 30–50 mg/kg during the acute febrile phase; once inflammation is reduced, a low antiplatelet dose of 3–5 mg/kg is used (see Table 46.3) [18].

The role of corticosteroid therapy in KD remains controversial; a meta-analysis found data indicating that corticosteroid therapy does not increase the incidence of CALs in high-risk children or patients refractory to IVIG therapy. Although the use of steroids did not significantly reduce the risk of CALs in children with KD, the data in the meta-analysis suggested that it does shorten the duration of fever and reduces the number of patients requiring retreatment with IVIG or other pharmacologic protocols [19]. Other therapies with immunosuppressive agents or anti-TNFα have been reported in isolated case reports or small series but cannot be recommended systematically [18].

Table 46.3 Treatment recommendation for KD [18]

Treatment	Dosage	Recommendations
IVIG	2 g/kg	Single infusion over 10 h
Aspirin	30–50 mg/kg	Maintain dose until fever goes down, then 3–5 mg/kg
Corticosteroids[a]	2 mg/kg IV prednisolone	For 5–7 days, then oral prednisone taper the dose over 2–3 weeks

[a]Only selected patients: IVIG resistant, severe/high risk patients or patients who already had coronary and/or peripheral aneurism with ongoing inflammation at presentation

Conclusion

Early recognition and treatment of KD are key to prevent heart complications of the disease. Attention should be paid to certain typical skin and mucous membrane manifestations, including the lip erythema and the perianal rash. Atypical cases of KD, in whom diagnostic criteria are not fully met, should be considered for treatment.

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Part X

Regional Ethnic/Racial Pediatric Dermatology

Traditional Chinese Medicine in Dermatology

47

Jean Ho and Poh Hong Ong

Abstract

Traditional healing or medicine refers to the "knowledge, skills and practices based on theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness" (Traditional Medicine. [Internet] World Health Organization. 2014. Available from: http://www.who.int/topics/traditional_medicine/en/).

Traditional Chinese medicine (TCM) is an important system of traditional medicine that has been in practice for more than 3,000 years. It has helped to maintain health and relief ailments for millions of people in Asia, long before the advent of modern medicine.

Keywords

Traditional Chinese Medicine • TCM • Historical perspective • Skin diseases

Introduction

Traditional healing or medicine refers to the "knowledge, skills and practices based on theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness" [1].

Traditional Chinese medicine (TCM) is an important system of traditional medicine that has been in practice for more than 3,000 years. It has helped to maintain health and relief ailments for millions of people in Asia, long before the advent of modern medicine.

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Historical Perspective

The earliest references to skin diseases [2, 3] were scattered among various works and artifacts. Inscriptions on bone excavated from the Shang dynasty (c. 1700–1100 B.C) were thought to describe a skin condition akin to scabies. The Yellow Emperor Inner Classic represented the culmination of medical knowledge during the Spring-Autumn and Warring States periods (c. 770–221 B.C). Signs and symptoms of various skin diseases were chronicled in remarkable detail, and attempts were made to elaborate on their likely etiology in relation to the four seasons.

Imperial physician Zhang Zhong-Jing of the Han Dynasty expanded on the earlier texts and wrote the *Discussion of Cold-induced Disorders* (c. 196) and *Concise Prescriptions from the Golden Casket*. Skin disorders such as urticaria and exfoliative dermatitis were mentioned. It also contained the first historical account of an ailment characterized by mouth, eye, and genital lesions which bore striking resemblance to what is presently known as Behcet's syndrome.

This was taken a step further in the *Discussion of the Origins of Symptoms of Diseases* (c. 610), in which Chao Yuan-Fang alluded to the entity of contact dermatitis.

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Followed by Sun Si-Miao in *Thousand Ducat Formulas* in which he described in great detail his observations of leprosy, making him the first leprosy expert of his time. The first comprehensive compilation in *Precise Treatment of Patterns* (c. 1602) by the Ming Dynasty physician Wan Ken-Tang categorized skin disease according to anatomical regions and described them in such detail that it became the de riguer text. The first atlas of skin disease, *Profound Insights on External Disease*, was penned (c. 1604) by Shen Dou-Yuan.

Up till the opium war (c. 1840), much of the people of China relied on TCM for healing and disease prevention. Following the influx of western influence, modern medicine was introduced into China. However, despite the increasing influence of modern biomedical science, TCM continued to remain an integral part of the psyche of the commoner. Schools and institutions specializing in TCM were continually being established. In fact, modern technology has accelerated TCM research [4], and methods of diagnosis and treatment were improved through the integration of traditional and modern medicine.

Principles of TCM

TCM differs in substance, methodology, and philosophy from modern medicine as we know it. It is not surprising that Western doctors continue to harbor misgivings about TCM and its standards.

In essence, TCM views the human body as an entity in equilibrium [3]—comprising a system of *qi* (energy) and *yin-yang* (balance). Although the concept may seem strange to western practitioners, TCM draws a parallel with well-established scientific concepts of metabolism (analogous to *qi*), immunity, and homeostasis (analogous to *yin-yang*).

TCM respects the holistic approach to health and the interrelationship of the mind, body, and the environment. Despite disease manifestations being external, their root causes are complex and involve the internal imbalance between yin and yang. In healthy individuals, yin and yang are in balance, and illness occurs when there is imbalance. The Chinese also recognize five elements: earth, water, fire, wood, and metal. These elements undergo transformative phrases that can affect one another. Each element is related to specific organs. In general, dysfunction of organs leads to various diseases. TCM recognizes the flow of *qi* through the body and identifies excess or deficiency of *qi* "as an important factor to the lead up of a disease."

Pathogenic Factors

Internal Causes

Emotional

The seven pathogenic emotions are elation, worry, anger, pensiveness, sadness, fear, and terror. Under normal conditions, these physiological phenomena will not cause disease. However, if the emotions are too stressful and constant, or the patient is too sensitive to stimulation, then they may induce acute and long-term changes that result in diseases. Pathogenic emotional factors are considered capable of disturbing the functional activities of *qi*, for example, according to an ancient saying, "Anger makes the *qi* rush upward, overjoy makes the *qi* circulate slowly, grief consumes *qi*, fear cause qi to flow downward, fright makes *qi* flow disorderly, overthinking leads to *qi* stagnation."

Improper Diet

Diet that is too spicy or high in fats is believed to cause dysfunction of the spleen, resulting in internal build up of toxin, leading to conditions such as acne, furuncles, and carbuncles.

Imbalance of Activity and Rest

Overwork consumes *qi* resulting in fatigue, whilst overly sedentary lifestyle causes *qi* stagnation.

Intolerance

Some individuals are constitutionally more sensitive to exposure to various factors. This is seen in conditions such as contact dermatitis, caused by hypersensitivity to substances coming into contact with the skin, and urticaria, which displays intolerance, for instance to certain drugs, foods, or airborne substances.

External Causes

Six Excesses: wind, cold, heat, dampness, dryness, fire.

Spring-wind, summer-heat, summer-fire, later summer-dampness, autumn-dryness, and winter-cold are the six variations in the climate of the four seasons. They are also known as the "six climatic factors" or the "six exogenous *qi*."

The human body has the ability to adapt to climatic variations. However, when bodily resistance is too low to adapt to climatic changes or if there is an abnormal altering of the weather which surpasses the body's adaptability, then disease occurs. These forms of climatic *qi* are all considered to be exogenous pathogenic factors.

Diseases which are not caused by exogenous pathogenic factors, but have symptoms similar to the syndromes of wind, cold, summer-heat, dampness, and dryness are termed internal heat, internal damp, internal dryness, and internal fire. These endogenous pathogenic factors are the outcome of dysfunctions of the organs.

Wind is a significant etiological factor in TCM methodology. It is often described as a vehicle that delivers external triggers deeper into the body, thus aggravating disease states. It potentiates the other climatic factors of dryness, dampness, and heat. Examples of skin disease that are related to wind include urticaria, pruritus, eczema, and seborrheic dermatitis. Internal wind is connected to liver; therefore TCM physicians would focus treatment on nourishing the blood and liver.

Cold causes stagnation of blood and *qi.* In extreme cases, cold causes blood stasis resulting in cold-induced injuries such as chilblain and panniculitis. Internal cold results from imbalance of *yin-yang* and loss of internal heat.

Heat, which is more prevalent during the summer months, results in increased sweating and loss of body fluids. Acute heat-related conditions include miliaria.

Dampness occurs when individuals are exposed to damp or wet environments. Due to the "sinking nature" of damp, it is often accompanied by heaviness and fatigue of the limbs. On the other hand, internal dampness is often caused by dysfunction of the spleen's functions, resulting in symptoms such as intense itching, swelling, or blistering.

Dryness predominates during the autumn and winter seasons and is termed cold-dryness, while prolonged dry spell in summer leads to warm-dryness. Skin diseases caused by dryness causes skin to crack and scale. The hands, feet, and mucous membrane are the most susceptible. Dryness arising from internal source is believed to be related to lung insufficiency which results in internal heat, thereby consuming body fluids. Prolonged use of bitter medicine can also result in internal dryness.

Fire and heat arise from excess of *yang*. Heat may be climatic as in wind-heat, dry-heat, or damp-heat. On the other hand, heat can be produced internally as a result of organ dysfunction or overstimulation of emotions. Skin diseases that are believed to be caused by internal heat include aphthous ulcers, shingles, acne, rosacea, and melasma.

Pestilences

Diseases that were contagious "through the mouth and nose" were described as early as the Ming dynasty by Wu You-Xing in his *Treatise on Febrile Pestilences* (c. 1642). The treatise notably included small pox, chicken pox, and rubella.

Arthropods and Parasites

These are divided into insect bites and stings, visible parasites such as mites and lice, and microscopic parasites such as leprosy and leishmaniasis.

Physical Agents

These include skin disorders arising from cuts, burns, and physical trauma.

TCM Methodology in Dermatology

- **TCM emphasizes a holistic approach in the diagnosis and management of diseases.**

- **TCM seeks to identify and correct the imbalances of a person's constitution which contribute to outward manifestation of disease.**

- **TCM may have an adjunctive role in treatment of chronic skin diseases for which the pathomechanism is not completely understood, and satisfactory cure is currently unavailable.**

TCM uses a holistic approach in the diagnosis and management of disease states. Therapy is not skin focused, but body focused. Therefore, the TCM practitioner always seeks to identify the inadequacies in a person's constitution that have resulted in imbalance of the core elements of a person's well-being.

While western medical science is progressively becoming more subspecialized, more organ specific, and categorical, TCM in contrast emphasizes the patient as a whole entity. It respects the influence of both intrinsic and extrinsic forces in the induction of disease and restoration of health.

Physical examination comprises of inspection of the patient's skin, complexion, physique, and tongue condition. Next the patient is questioned on various symptoms: if he is hot or cold; sweating, thirst, appetite, stools, and so forth. Finally, the TCM practitioner palpates the patient's wrist to feel the quality of the pulse so as to assess overall health.

TCM diagnosis is a syndrome complex that describes the imbalances of the elements. For example, an eczema patient could be having a damp-heat pattern, while another eczema patient could be experiencing a *qi* deficiency syndrome, yet another patient with eczema could belong to the fire-heat syndrome. The TCM practitioner would then prescribe a treatment regimen according to the disease pattern (Table 47.1).

TCM Treatment with Herbs

Skin diseases are considered an outward manifestation of dysfunction of the organs, channels, and bodily substances (*qi*, blood, and fluids). Therefore treatment includes external

Table 47.1 Principles of TCM dermatological diagnosis

Presenting complaint	Nature, site duration
History of presenting complaint	Details of onset; signs, symptoms and distribution; course (acute, relapsing, chronic); generalized symptoms; previous treatments; dietary history; menstrual history; occupational history; seasonal
Medical history	Present and previous medical conditions, operations, allergies, medications, drug intolerance
Patients' personal history	Race, occupation, hobbies, diet, emotional status, family history
Examination of skin lesions	Location and distribution; inspection of lesions characteristics; examine other areas (e.g. mouth, tongue, behind ears, scalp)
Laboratory analysis	If diagnosis cannot be reached from above stated methods, skin biopsy and/or laboratory test may be required[a]

[a]Note: this is increasingly used, as the integration of TCM and western medicine becomes more prevalent

application of medication as well as systemic therapy using oral herbal medicines.

The utilization of herbal medicines [5] to tonify the body and restore health is a concept that vastly differs from the practice of modern medicine. Modern drugs are largely single-entity compounds designed to treat specific conditions. They are highly successful in addressing acute conditions, such as infections, in a fast and predictable manner. This leads to a favorable outcome within the shortest period of time. In contrast, TCMs are decoctions of up to 20 different types of herbs that are customized for different patients. The principle is restoring and maintaining balance. This approach is more appropriate to disease prevention and the treatment of chronic diseases, where western medicine has only been able to alleviate. Most Chinese formulations contain a mixture of herbs. There are different methods of classifying the ways in which these can be combined. When combined, two biologically active substances can be observed to have the following effects: mutual accentuation, mutual enhancement, mutual counteraction, mutual suppression, and mutual incompatibility. The principal ingredient is a substance that provides the main therapeutic thrust; the second principal ingredient enhances or assists the therapeutic actions of the first. The rest serve to treat accompanying symptoms, moderate the toxicity of the primary herbs, or exert a harmonizing effect.

Internal Treatment

Decoctions

Decoctions are prepared by placing medicinal herbs in water or other liquids (e.g., wine) and boiled for a specified length of time. The liquid is then ingested. Decoctions are absorbed quickly by the body and are able to exert an immediate onset of action.

Pills

Pills are prepared by combining finely powdered herbs for ease of consumption and storage, as well as standardization of dosages.

External Treatment

Powders

These are usually prepared by grinding together dried medicinal substances into a powder of fine consistency. They are either sprinkled directly on the affected area or combined with medicinal herbs to make a poultice. They function to disinfect, reduce inflammation, remove necrotic tissue, and promote wound healing.

Washes

Washes are prepared by decocting herbs, then applying the liquid as a swab, compress, or bath. They provide soothing relief for itch and pain, reduction of exudation.

Ointments

Ointments are prepared by combining powdered herbs with a greasy vehicle such as petroleum jelly. They are rubbed on the affected areas to lubricate and protect dry skin, barrier effects, and promote healing.

Plasters

Plasters are oil- or wax-based medications affixed onto a backing material and then applied topically. They can exert external effects such as promote suppuration, promote healing, or clear necrosis. They can also exert an internal effect to harmonize the *qi* and blood, dispel wind and cold. Administration of plasters is known to cause allergic contact dermatitis in sensitized individuals.

TCM and Atopic Dermatitis

Historical Perspective

The earliest record of eczema was that of "milk ringworm," which most resembled infantile dermatitis. This dated back to the Sui Dynasty (c. 581–618 A.D).

Later during the Qing dynasty (c. 1644–1911), the "four bends wind" concept was presented. As the name suggested, eczematous skin lesions occurred in the flexural aspects of the arms and legs. Extreme itching and recurrent episodes with copious oozing were included in the description. Subsequently, other dermatitis subtypes such as seborrheic dermatitis, scrotal eczema, and hand eczema were described in significant detail.

The Chinese term for eczema translates directly to "damp rash." This is derived from the exudation seen in acute eczema. TCM attributes this to internal imbalances, leading to excess dampness and heat. According to TCM, atopic dermatitis (AD) is caused by a congenitally "weak" constitution, which predisposes the individual to extrinsic aggravators such as dietary, lifestyle, and climatic changes. As eczema becomes recurrent and chronic, excessive dampness is said to consume the blood and body fluids (immunological dysfunction), generating dryness, dyspigmentation, and lichenification. At the organ level, AD is also related to dysfunction of the spleen and stomach.

Therefore, while western diagnosis is skin limited, TCM diagnosis strives to clarify the disease syndrome complex underlying it, according to the principles of TCM discussed above.

The Increasing Appeal of TCM

To date, AD remains a frustrating disease for both patients and doctors alike. As the pathophysiology of AD has not been fully established and there is no apparent cure, treatment has been largely symptomatic. Therapy has, thus far, focused on relief of flares with topical corticosteroids and calcineurin inhibitors, as well as skin barrier therapy with emollients. More severe disease would necessitate oral corticosteroids and immunosuppressive agents, which are associated with significant risk of adverse events.

The limitation of western medicine has prompted increasing number of patients to turn to TCM [4], in part due to the perceived safety of TCM by patients and in part due to the appeal of pedagogy of TCM in restoring balance and potentially curing the disease.

However, the complexities of herbal decoctions and granules, the different routes of administration, and auxiliary treatments such as acupuncture and massage have proven daunting for western doctors to regard TCM with any amount of credibility. It also does not help that early studies were mainly found in Chinese publications, thus reducing accessibility. With the need for more objective evidence and validation, TCM is now being extensively studied in clinical trials and pharmacological studies.

Herbs [3] such as Cortex Moutan Radix (Danpi), Radix Paeoniae Alba (Bai Shao), *Potentilla chinensis* Ser (Weilingcai), and Radix Glycyrrhizae (Gan Cao) are common treatments for allergy. Flos Lonicerae (Jinyinhua) and Herba Menthae (Bohe) clear 'damp-heat' from the exterior; Cortex Moutan (Danpi) clears 'heat' from blood while Rhizoma Atractylodis (Cangzhu) and Cortex Phellodendri (Huangbai) clear the 'damp-heat' from the interior. Pharmacological studies indicate that these herbs have anti-allergic, anti-inflammatory, and sedative action for relief of itchiness.

Clinical Efficacy

To date there are seven randomized controlled trials [6] (one comparing Chinese herbal medicine and western medicine with western medicine alone; six comparing Chinese herbal medicine with placebo) and more than 200 clinical trials investigating the efficacy of TCM in AD.

Cheng et al. [7] studied the efficacy of a common herbal preparation Xiao Feng San (comprising of *Glycyrrhiza uralensis* (Gancao), Saposhnikovia Divaricate (Fangfeng), *Schizonepeta tenuifolia* (Jingjie), *Atractylodes lancea* (Cangzhu), *Angelica sinensis* (Danggui), *Rehmannia Glutinosa* (Dihuang), *Clematidis Armandii* (Chuanmutong), *Cryptotympana pustulata* (Chantui), *Linum usitatissimum* (Yamazi), *Anemarrhena asphodeloides* (Zhimu), Gypsum Fibrosum (Shigao), *Sophora flavescens* (Kushen), *Articum lappa* (Niubangzi)) commonly used in the Asian context for the treatment of AD. In a double-blind, randomized control trial of 71 patients (8–23 years) with severe AD affecting >20 % body surface area, there were statistically significant improvement in pruritus, erythema, surface damage, and sleep scores. No side effects were experienced in all the patients, suggesting that TCM would be a potentially beneficial and safe adjunctive therapy for patients with recalcitrant AD.

Huang et al. [8] found a combination of western medicine and TCM to be superior to western medicine alone in children aged 3–11 years, in improving clinical scores. Shi et al. [9] demonstrated that the TCM Jiawei Danggui decoction improved AD scores through modulation of inflammatory cytokines such as IL-4, IL-10, and IL-12. More recently, an open-label clinical study [10] involving a novel combination of oral and topical TCM therapy in 94 patients showed significant improvement in severity of AD. Serum IgE level and eosinophil counts were significantly reduced at the end of the study.

Two randomized placebo-controlled trials [11, 12] were performed to study the effects of Zemaphyte, a decoction of ten herbs useful for treating AD characterized by erythema, lichenification, and plaques of dermatitis in the absence of active exudation or clinical infection. The ten herbs used were *Lophatherum gracile* (Danzhuye), *Potentilla Chinensis* (Weilingcai), *Tribulus terrestris* (Jili), *Rehmannia glutinosa* (Dihuang), *Clematidis armandii* (Chuanmutong),

Ledebouriella Saseloides (Fangfeng), *Dictamnus dasycarpus* (Baixianpi), *Paeonia lactiflora* (Baishao), *Schizonepeta tenuifolia* (Jingjie), and *Glycyrrhizia Glabra* (Gancao). These herbs were placed in sachets and boiled to make a decoction that was orally administered daily as a tea. The placebo consisted of a decoction made from several herbs with similar smells and tastes that have no known efficacy in AD. The first study involving 47 children demonstrated a median decrease in erythema score of 51 %, in the treatment group compared with only 6.1 % improvement in the placebo group. The percentage surface involvement also decreased by 63.1 % and 6.2 % for the herb-treated and placebo groups, respectively. No serious adverse effects were found. These children were offered continued treatment, with 18 children completing 1 year of treatment and showed 90 % reduction in eczema activity scores. By the end of 1 year, seven children were able to discontinue therapy without relapse. Asymptomatic elevation of alanine aminotransferase level was noted in two patients, levels returning to normal after discontinuing treatment. Although the sample sizes were limited, results were promising for patients with persistent disease. It should be emphasized that although no serious adverse effects were noted in this study [10], careful monitoring of complete blood cell count and liver function is recommended, as liver failure and even death have been reported with these TCM herbs. However, in a separate study [13] involving 40 patients, investigators did not observe any benefit of Zemaphyte in recalcitrant AD. So far, the sample sizes of these studies are too limited for any real conclusion to be made, and more robust studies are required.

PentaHerbs a proprietary capsule comprising of five different herbs, *Paeonia suffruticosa* root bark (also known as Cortex Moutan), *Phellodendron Chinensis* bark (Chuanghuangbai), *Lonicera japonica* flower (Jinyinhua), Mentha Herba aerial part (Bohe), and *Atractylodes lancea* rhizome (Cangzhu), was found, in a randomized, double-blind, placebo-controlled study [14], to have beneficial effects on improvement of eczema SCORAD and Children Dermatology Life Quality Index (CDLQI) scores. The use of topical steroid [15] was also reduced by one-third. However, no significant difference in overall clinical scores was found. The PentaHerbs formulation was tested for contaminants [16] such as heavy metals or corticosteroid and found not to contain any. In a separate study [17], the herbal formula, Hochu-ekki-to (comprising of Radix Astragali (Huangqi), Panax Ginseng (Renshen), Rhizoma Atractylodis (Cangzhu), *Glycyrrhiza uralensis* (Gancao), *Angelica sinensis* (Danggui), Citri Reticulatae (Baomazipi), Rhizoma Cimicifugae (Shengma), Radix Bupleuri (Chaihu), Zingiber Officinale (Jiang), Fructus Jujubae date (Dazao)) was found to reduce the total equivalent amount of topical corticosteroid usage by 50 % during a 6-month period in a multicentre, randomized, double-blind, placebo-controlled study. However, again there was no statistically significant difference in skin severity scores.

It is important to note that the combinations of herbs used in the various studies were different, giving rise to different pharmacokinetics and pharmacodynamics. There are also concerns that the varied geographic sources of the herbs used in different studies could also have affected the active compounds. Therefore, more RCTs and rigorous pharmacological studies are necessary for stronger evidence regarding efficacy of TCM.

In Vitro Studies

It is known that the specific herbs [18–20] used in these studies have anti-inflammatory, antibacterial, antifungal, antihistaminic, immunosuppressant, and corticosteroid-like effects. Several studies have attempted to elucidate the mechanism of action of individual herbs and their combined effects.

Oral administration of *Gypsum fibrosum* was shown to increase cutaneous water content in mice [18] via the upregulation of aquaporins. Gypsum fibrosum is a common TCM herb given to relieve "heat," characterized by excessive thirst, sweating, fatigue, poor concentration, pruritus, and dry skin, in the body.

Bakumijiogan, a unique TCM herbal formula, comprising of eight herbs, Rehmannia Radix (Dihuang), Cornus Fructus (Shanzhuyu), Dioscoreae Rhizoma (Shanyao), Alisma Rhizoma (Zexie), Poria Sclerotium (Fushen), Moutan bark (Mudanpi), *Ophiopogon japonicus* tuber (Maidong), *Schisandra chinensis* fruit (Wuweizi), was shown to reduce swelling of AD lesions [21] in Nishiki Nezumi Cinnamon (NC) mouse models. This effect was attributed to the down-regulation of the T-helper 2 cytokines, namely interleukin-1α (IL-1α) and tumor necrosis factor TNF-α.

PentaHerbs is a formula comprising of five different herbs, which were individually assessed for their effects on mast cell activity. Each herb was found to have various modulating effects on mast cells [18], which included the inhibition of histamine release from mast cells and prostaglandin D2 synthesis. PentaHerbs decreased plasma levels of brain-derived neurotrophic factor (BDNF) and thymus and activation-regulated chemokine (TARC) in children with AD. PentaHerbs suppressed mRNA transcription of BDNF, TARC, interferon-γ, and tumor necrosis factor-α [19] by cultured peripheral blood mononuclear cell (PBMC). These immunomodulatory properties are believed to contribute to the clinical efficacy in AD treatment.

The bark of the birch tree (*Betula platyphylla* var. Japonica) which is used to treat AD, was studied in NC/Nga mice models [21] for AD. The herb decreased scratching and skin inflammation, as well as immunoglobulin E and interleukin-4 messenger ribonucleic acid (mRNA) levels. The findings suggest that the herb exerts some effect on the suppression of the T-helper 2 cellular response in AD. In the Zemaphyte trials [22], biopsy specimens were obtained from the lesional skin of patients treated with the herbal combination. The investigators observed

a statistically significant reduction in CD23 antigen-presenting cells, compared with nonlesional skin.

Indigo Naturalis (Qingdai) [23], a dark-blue powder prepared from the leaves of plants such as *Baphicacanthus cusia*, *Polygonum tinctorium*, *Isatis indigotica* and *Indigofera tinctoria*, exhibits antiviral, antibacterial, and antitumor properties. It is used in treatment of various inflammatory and infectious diseases, e.g., eczema, aphthae, erysipelas, and herpes zoster. Due to its apoptotic effect [24] and ability to modify the proliferation and differentiation of keratinocytes, it is commonly employed in the treatment of psoriasis. Moreover, indirubin [24], one of the active compounds, has been shown to inhibit the production of interferon-γ, interleukin-6, and RANTES chemokine, involved in psoriasis pathogenesis.

Radix Salvia Miltiorrhiza (Danshen) [25] contains a variety of deterpenoids, phenolics, flavonoids, triterpenoids, and sterols. Its active components have anti-ischaemic, antioxidant, and antitumor activity. It has a significant inhibitory effect on the production of IFN-γ from lymphocytes and IL-12 from macrophages as well as suppression of mast cell degranulation. This herb is thought to exhibit some hepatoprotective effect [26], which is in part due to its ability to improve blood circulation and promote regeneration of liver cells.

Glycyrrhiza uralensis (Gancao) [27], may have protective effect on hepatocytes and gastrointestinal tract, is commonly used as component of various antipsoriatic and anti-eczema preparations. It is believed to prevent side effects commonly observed in the process of herbal therapy application. Moreover, it exerts both immunosuppressive and immune-enhancing activities, which may modulate abnormal immunological processes in eczema. *Rehmannia glutinosa* (Dihuang), a frequent ingredient in herbal formulas, is a Chinese herb use in the treatment of eczema and psoriasis and various dermatoses. In animal models [28], the root of *Rehmannia glutinosa* is capable of inhibiting the release of histamine and production of TNF-α and IL-1, and therefore having a positive effect on the treatment of eczema and psoriasis.

Radix Angelicae (Danggui) [29] is regarded as an effective agent in treatment of acne, headache, toothache, sinusitis, colds, and flu. It contains furocoumarins [30], actively involved in the inhibition of cyclooxygenase and lipoxygenase pathways of arachidonate metabolism. Since Angelica species are sources of psoralens, they are applied both systemically and topically in psoriasis. The herb is capable of inducing phototoxic reactions in some individuals.

TCM as an adjunctive treatment [31] has been reported to benefit the patients with several other dermatological conditions such as alopecia totalis, Behcet's disease, psoriasis, and scleroderma (Fig. 47.1).

Fig. 47.1 (**a**–**d**) Common TCM herbs used in dermatology. (**a**) *Dictamnus Cortex* (**b**) *Radix Astragali* (**c**) *Smilacis Glabrae Rhizoma* (**d**) *Lonicerae Flos*

Adverse Effects of TCM Herbs

Adverse effects to Chinese medicines [32–34] can develop due to response to natural compounds, natural toxins, or to contaminants and adulterations, for example arsenic, steroids, diazepam, diuretics, NSAIDS, and caffeine.

Adverse reactions during treatment range from mild (transient hepatitis, dermatitis) [7] to severe or fatal illnesses (liver failure, anaphylactic shock) [10]. Derangement of liver function is one of the most commonly documented adverse effects of TCM preparations. Moreover, since numerous herbal formulations contain psoralen [34], a photosensitizing compound, their use can result in photosensitivity.

Xu et al. [35] reported a patient who developed lichen planus pemphigoides a few weeks after taking an oral preparation of Chinese herbs. Lim et al. [33] described cases where patients presented with severe cutaneous adverse drug reactions to TCM. One of the patients developed toxic epidermal necrolysis after consuming an unknown TCM powder. Another patient developed allergic contact dermatitis to topical liniment which was later found to contain coumarin, piroxicam, and salicylates. A patient with psoriasis experienced aggravation of skin lesions and hepatitis after consuming TCM adulterated with phenylbutazone and dexamethasone. Wu et al. [36] reported a fatal case of severe adverse drug reaction in a patient with AD who was using arsenic-containing topical herbal ointment over the whole body. As a result, eczema patients who are steroid phobic [37] and shun western medicine in favor of the presumably more "natural" TCM, may be unknowingly exposing themselves to higher cumulative amounts of topical or oral steroid masquerading as TCM.

Acupuncture

Acupuncture is widely used either alone or in conjunction with oral therapy in the treatment of dermatological conditions such as urticaria, eczema, and neurodermatitis. Acupuncture involves the placement of fine needles along specific points along the meridians [38] so as to relieve excess elements, and tonify deficiencies. In TCM, meridians serve as channels through which energy *qi* is believed to flow through.

In the relief of pruritic dermatoses [39–41], acupuncture reduces itch and wheal response following intradermal histamine injection. It was as effective as oral cetirizine in reducing Type 1 hypersensitivity itch in patients with AD, without causing somnolence and diminished attention focus as seen in the cetirizine group. Acupuncture demonstrated greater itch-abortive effect [42] during peak itch intensity compared to cetirizine. Twice weekly sessions of acupuncture, in combination with Chinese herbal medicine, was found to be reduce Eczema Area and Severity Index and Dermatology Life Quality Index scores [43] in a case series of 20 patients with mild to severe AD.

A possible mechanism for the antipruritic effect of acupuncture is the counterirritation or distraction theory [44], which has been largely studied for analgesic properties of acupuncture. Another plausible explanation might relate to mediators associated with itch [45], such as endogenous opioid peptides. Beta-endorphin and other similar neuromodulators have been implicated in acupuncture analgesia and have been shown to influence itch sensation. On a spinal level, acupuncture seems to have a counterirritation effect via the reduction of prostaglandin E2 levels in brain [46] and serum of lipopolysaccharide (LPS)-injected rats. Prostaglandin E2 is a mediator involved in itch and potentiates the flare reaction to histamine. In a separate study [47], reduction of itch in acupuncture was found to be associated with reduction of allergen-induced basophil activation in AD patients. Neuroimaging studies [48] have demonstrated that acupuncture modulates the limbic and paralimbic brain structure, such as the amygdale, anterior cingulated, and insular cortices, known to process itch sensation in both healthy adults and AD patients.

The most common complications reported following acupuncture treatment were cutaneous infections. Mycobacterial and staphylococcal infections were reported. Most of these cases were caused by reusable needles. Other infective complications included septic arthritis, facial erysipelas, and necrotizing fasciitis. Rarely, acupuncture treatment has resulted in organ or tissue injury [49] such as pneumothorax, peripheral nerve injury, spinal cord injury, pseudolymphoma, and pyoderma gangrenosum. Encouragement of conscientious reporting of adverse outcomes following acupuncture by practitioners, and formal training on safe practices and infection control, would reduce complication rate while maximizing patient benefits.

It remains to be further confirmed if acupuncture offers any true benefit in the clinical management of pruritic skin conditions such as AD and chronic urticaria. High-quality RCTs and biomedical research are needed for stronger evidence regarding its efficacy and safety (Fig. 47.2).

Massage Therapy

The traditional art of massage therapy according to the rules of TCM is referred as Tui Na. The technique comprises of various maneuvers such as pushing, kneading, circular rubbing, pinching, and finger pressure. These are performed over the specific pressure points (acupoints) that are located at different parts of the body, along the Meridian lines.

A study involving 240 Chinese infants [50] with AD, who were randomly assigned to massage therapy versus standard

Fig. 47.2 Acupuncture

therapy, reported both short- and long-term benefits, which were comparable to standard treatment arm. Lower rate of disease recurrence was also observed in the massage therapy group. Twenty children were studied in a randomized, controlled trial comparing standard eczema treatment versus standard treatment and daily 20-min massage sessions. Improvement in symptoms such as pruritus and excoriation, as well as anxiety scores and coping ability were observed. Increased coping ability [51] of the patient in the setting of a chronic disease would be a desirable goal of therapy. Massage therapy likely benefits AD by reducing stress while promoting enjoyable interaction between parent and child, hence improving compliance to topical treatment. The appeal of massage therapy is that it is easily taught to the parent or caregiver, incurs minimal financial cost, and is not known to have any adverse effects. However, it remains unclear whether massage therapy has any true benefit on the overall disease activity (Table 47.2).

Cupping

Glass cups are heated to create a partial vacuum over the skin. The underlying tissues are drawn up and local blood stasis is induced. This is seen as circular areas of ecchymoses on the skin. Conditions which have been found to respond to this therapy include eczema, pruritus, recurrent carbuncles, or furunculosis. Despite the sizeable clinical experience from experts within the field, the present lack of controlled studies remains a main drawback for these methods (Fig. 47.3).

Table 47.2 Common acupoints used in treating skin diseases

Meridian points	Location	Skin diseases
LI-11	Lateral aspect of flexed elbow, corresponding to the head of brachioradialis muscle	Urticaria, dryness of skin
LI-4	On the dorsum of the hand, between the 1st and 2nd metacarpal bones	Urticaria, facial edema, pain
ST-36	On the anterior lateral side of the leg, one finger breadth from the anterior crest of the tibia	Skin allergies
SP-6	On the medial side of the leg, 3 cm above the tip of the medial malleolus, posterior to the medial border of the tibia	Eczema, urticaria, neurodermatitis
GV-14	The posterior midline, in the depression below the spinous process of the 7th cervical vertebra	Eczema, urticaria
CV-6	On the lower abdomen and on the anterior midline. 1.5 cm below the centre of the umbilicus	Eczema, urticaria, neurodermatitis
BL-40	At the midpoint of the popliteal crease, between the tendon of the biceps muscle of the thigh and the semitendinosus muscle	Furuncles, impetigo

Fig. 47.3 Cupping

Future Development and Research

Modernization of Traditional Medicine

TCM encompasses a wide range of practices including some that are familiar to the West, such as herbal medicine and acupuncture, as well as others that remain peculiar to most Westerners such as cupping (heated cup therapy), tuina (massage), qigong (movement and breathing exercises), and moxibustion (burnt mugwort therapy). Investigation into whether these therapies have underlying mechanism of action is now a central task in TCM research.

With more quality controlled trials, characterization of the pharmacokinetics of complex herbal formulations, chemical profiling, and biological assays, it is foreseeable that TCMs credibility stands to increase in the future.

In Hong Kong and China [52], 60 % of the population has consulted TCM practitioner at least once. According to national survey data, as high as 75 % of population in Singapore, Taiwan, South Korea, and Japan used traditional medicine once a year. United States and Europe are experiencing growth in TCM use with imports of TCM products increasing 10 % per year. In the light of increasing recognition of TCM by the World Health Organization (WHO), countries are pursuing integration of traditional medicine with modern medicine. In the white paper presented, WHO highlighted the need to depart from the current apprentice-master training of TCM, moving towards standardization of its education and practice. In 2008, WHO endorsed an international agreement [53] drawn up in Beijing to support the safe and effective use of TCM in modern healthcare. This would ensure that TCM is correctly employed to treat patients, minimizing toxicity from inappropriate usage of herbal medicine. Formal training in TCM is currently offered in universities across the region such as Singapore and Malaysia. In Singapore, there are clinics offering TCM in all acute as well as community hospitals. In Malaysia, there are already twelve hospitals to date that offer both modern and traditional medicine.

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Skin of Aboriginal Children

48

John Su and Christopher Heyes

Abstract

The indigenous people of Australia (Aboriginal and Torres Strait Islander), Canada (First Nation, Inuit, and Metis People), USA (American Indians and Alaska Natives), and New Zealand (Māori) are geographically, genetically, and culturally distinct groups. Increased prevalences of many pediatric skin diseases are, however, common to indigenous people across these four countries. Other skin diseases are specific to the country of origin of an indigenous person. This chapter covers skin conditions common to indigenous people of Australia, New Zealand, USA, and Canada, but focuses particularly on skin diseases affecting Australian Aboriginal and Torres Strait Islander people. Apart from genetic factors and skin color, environmental, cultural, nutritional, and socioeconomic factors play important roles in disease pathogenesis and in determining the effectiveness of prescribed therapy. Infections represent the major burden of skin disease and they are often concomitant or atypical. Better awareness of specific risk factors and exposures, of the variations of skin signs resulting from different skin colors, and of cultural sensitivities (in history taking, communication and the implementation of management plans) will enable better clinical care.

Keywords

Indigenous • Rural • Ethnic • Cultural • Australia • Pediatric • Dermatology • Pyoderma • Scabies • Infection

Background/Introduction

The indigenous people of Australia (Aboriginal and Torres Strait Islander), Canada (First Nation, Inuit, and Metis People), USA (American Indians and Alaska Natives), and New Zealand (Māori) are geographically, genetically, and culturally distinct groups. Increased prevalences of many pediatric skin diseases are, however, common to indigenous people across these four countries, whereas other skin diseases are specific to the country of origin of an indigenous person. Although this chapter covers skin conditions common to indigenous people of Australia, New Zealand, USA, and Canada, it focuses particularly on skin diseases affecting Australian Aboriginal and Torres Strait Islander people.

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Self-identification and acceptance by the indigenous community are two necessary conditions of aboriginality. The community is itself defined by voluntarily perceived cultural distinctiveness, a shared (precolonial) history, and often a shared social experience of marginalization. The most widely adopted definition of aboriginality in Australia is known as the 'Commonwealth Working Definition'. It states that "An Aboriginal or Torres Strait Islander is (1) a person of Aboriginal or Torres Strait Islander descent, (2) who identifies as being of Aboriginal and Torres Strait Islander origin and (3) who is accepted as such by the community with which the person associates" [1]. Distinctions in pediatric dermatology conditions amongst indigenous people therefore only relate partly to skin color and genetic predispositions, but perhaps more importantly to particular environmental exposures, cultural practices, and socioeconomic circumstances.

Indigenous populations in Australia, New Zealand, USA, and Canada share a higher burden of infectious disease, higher infant mortality, and reduced life expectancy [2, 3]. Social disadvantage in the form of poverty, food insecurity, overcrowded housing, unemployment, substance abuse, high rates of truancy, family violence, child abuse, mental health morbidity, suicide, and incarceration may be overrepresented, resulting in a 'Fourth World' phenomenon ('Third World' inside the 'First World') [4–6].

Indigenous populations may also suffer a disproportionately high burden of disease across a range of conditions, including renal, cardiovascular, respiratory, and (especially) infectious diseases. The life expectancy of Australian Aboriginal men and women, for example, is 10.6 years and 9.5 years, respectively, lower than the nonindigenous Australian population [4]. The greatest burden of disease relates to endemic and epidemic infections occurring in Australian indigenous communities. Poverty, overcrowding, poor hygiene, high mobility, limited medical access, and poor compliance contribute to infectious skin disease [7, 8].

In Australia, 2.5 % of the population is identified as indigenous. However, higher indigenous representation is found in tropical and remote regions such as the Northern Territory where indigenous people represent almost a third of the population [9]. Particularly, high burden of disease can be found in remote indigenous communities in the Northern Territory, Queensland, and Western Australia. Whereas overall 25 % of all Australian Aboriginal children live in remote areas, this figure approximates 75 % in the Northern Territory [9, 10]. Skin disease is the second most common acute Aboriginal pediatric presentation to health services in remote Northern Australia (following respiratory disease) and the fourth most common (11 %) in a study of urban Australia (following respiratory, trauma, and gastrointestinal disease) [11, 12].

Predisposing Factors and Diseases

Genetic

Researchers suggest that ancestors of indigenous Australians may have migrated 40,000–60,000 years ago to what is now Australia, having mixed with Denisovans from Siberia and having received a Holocene gene flow from India en route from Africa [13, 14]. This population occupied the island with a high degree of isolation until European settlement occurred some 200 years ago, following which intermarriages with nonindigenous populations have increased genetic heterogeneity.

Ethical issues have limited indigenous population genetic studies. Genes recently identified distinguishing European and American indigenous genotypes affecting skin pigmentation include *SLC24A5*, *SLC45A2*, *OPRM1*, and *EGFR* [15]. The former two also distinguish European from both West African and East Asian genotypes. Indigenous Australian genotypes have not been extensively studied to date.

Skin color, however, is not unique in mediating genetic disease susceptibility, even for photosensitive conditions. For example, in indigenous Malaysians, skin lightening resulting from admixture with European genes confers UV susceptibility that is not seen when lightening is conferred by Asian genes, suggesting photoprotective mechanisms beyond the skin color [16]. Indigenous genetic determinants of susceptibility and immune response to infections and tendency to the development of autoimmune disease possibly play important roles. They are an area of ongoing study.

On the other hand, darker skin color in indigenous populations from Africa, the Americas, Asia, and Oceania appears to carry similar but not identical propensities to Mongolian spots, dermatosis papulosa nigra, melasma, postinflammatory dyspigmentation, papular eczema, and keloids. Likewise, darker skin color can affect the presentation of diseases, with erythema assuming violaceous and postinflammatory pigmentation-like appearances.

Physical

- **Traumatic skin changes in children include dorsal–lateral hyperkeratosis of the feet, lateral malleolar bursitis, ritual scarring, and nonaccidental injury**
- **Ochre (yellow, white, and red) and clay are commonly used in Australian Aboriginal cultural ceremonies**

Social and cultural factors contributing to indigenous skin changes are easier to discern. Central and Northern Aboriginal Australian children very commonly demonstrate bilateral, diffuse, lichenified, hyperkeratotic, and fissured

Table 48.1 Deliberate cultural trauma in Indigenous Australians [17]

Ritual	Subject	Instrument	Sign
Sorry cut	Men	Knife	Laceration of arms, thighs
	Women	Stone, club (nulla nulla), stick	Scalp laceration, scar, scarring alopecia
	Teenage girls	Knife	Laceration to hips and calves
Nice marks	Prepubertal and teenage girls	Glowing twigs, cigarettes	Burns on dorsal hands and forearms
Ceremonial	Various	Piercings	Nasal septum, earlobes
		Burning leaves	Posterior shoulder burns, scars

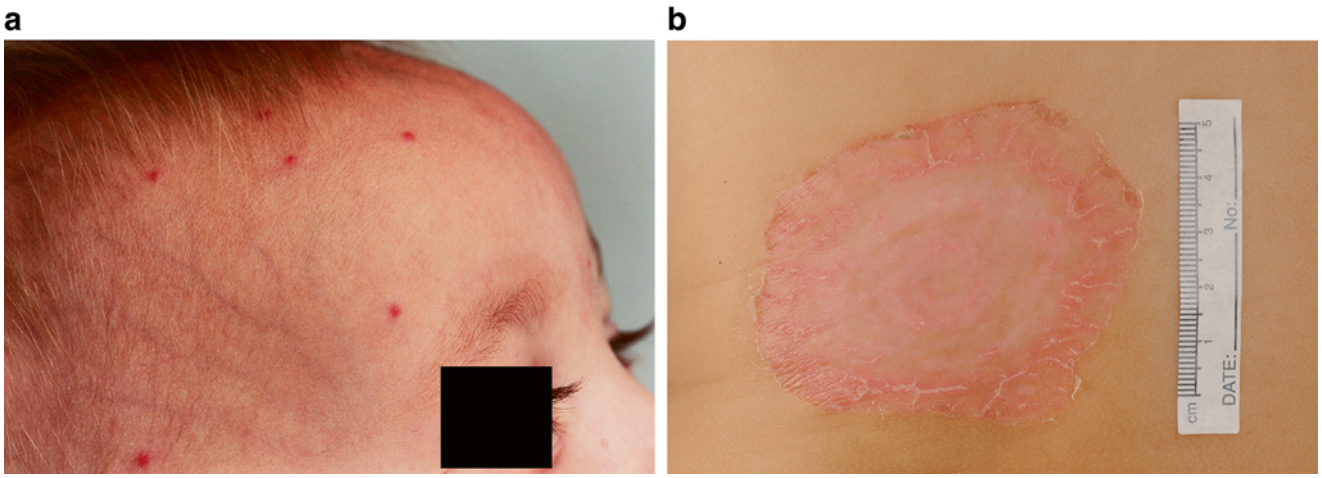

Fig. 48.1 Insect bites presenting as (**a**) clustered papules in exposed skin of a 9 month old boy and (**b**) as an isolated resolving bullous lesion in a boy in urban south-eastern Australia (Royal Children's Hospital Melbourne)

changes of the dorsolateral feet ("bush feet"), often associated with hyperkeratotic soles and callosities, induced by the trauma of walking barefoot. This can be confused with dried mud, terra firma-forme dermatosis and ichthyosis [17]. Similarly, residual scalp ochre following ceremonial coloring can be confused with scaling from psoriasis and seborrheic dermatitis, which are conversely, rarely seen in indigenous Australians. Lateral malleolar bursitis and secondary ulceration can follow prolonged periods of sitting cross-legged. Ulcers can also result from other lifestyle exposures, such as animals, stingrays, thorny plants, and smoking, as well as from intentional injury arising from disputes, abuse, or cultural rituals (Table 48.1) [17]. An Australian example of ritual injury is the 'sorry cut', a self-inflicted laceration reflecting personal sharing in a communal loss. They are inflicted by indigenous women at the loss of a partner and by girls to signify solidarity with the pain of a brother undergoing circumcision [17].

Environment

- **Plants and insects can cause persistent papular eruptions, local and systematized allergic reactions due to contact, foreign body reactions, toxins, and hypersensitivity.**
- **Betel nut and tobacco chewing and kava ingestion may begin in adolescence**
- **Water exposures may lead to contact hypersensitivity, toxic reactions, infestations, and infections.**

Plant and insect exposure can result in solitary, clustered, or patterned papular, urticarial or vesiculobullous changes and may subsequently result in secondary infection or allergic reactions that may be localized or generalized (Fig. 48.1). Common Australian pathogenic insects include midges (sandflies), mosquitoes, ticks, fleas, mites, black flies, march flies, leeches, blister beetles, and ants.

Bindii (Jo Jo) dermatitis results from impregnation of the spine of the bindii seed (*Soliva pterosperma*) into the skin, usually of palms, soles, elbows, knees, and buttocks of young boys during spring and summer [18]. Allergic and possibly foreign body reactions result in 1–2 mm red micropapules and papulopustules that may initially be itchy or tender, but often remain relatively asymptomatic for months, resolving towards winter and not responding to standard eczema treatments [18].

Other hairy plants that cause reactions include prickly pear, Hibiscus, *Malachra fasciata*, and *Cionachne cyathapoda* [17]. Plant contact allergy and toxic reactions (e.g. to latex from the Mangrove plant) are also more common in indigenous children, possibly because of increased exposure

[19]. *Caterpillar hair dermatitis* may be underdiagnosed in indigenous communities, characterized by recurrent papulourticarial reactions relating to airborne spread of hair. An indoor outbreak has been reported in Australia originating from an infested Eucalyptus tree [17, 20].

Older adolescents may adopt adult practices like betel nut and tobacco chewing and kava ingestion (kava is a sedative drink produced from the roots of the plant *Piper methysticum*). Betel nut and tobacco chewing can cause psychoactive and autonomic effects, gum and teeth staining, malignancies (oropharyngeal and pancreatic), peptic ulcer, and heart disease. Kava has been associated with a cephalocaudal progressive ichthyosis, facial edema, and hepatotoxicity [21].

Water hazards include coral dermatitis, starfish and sea-urchin toxic dermatitis, and reactions from fish and marine sponges. *Cercarial dermatitis* results from cutaneous penetration by avian or non-avian schistosomes (e.g. *Austrobilharzia terrigalensis*, *A. variglandis*), and it is characterized by severe itch of exposed skin. This contrasts with the pruritic papules under clothing that characterizes seabather's eruption from the nematocysts of larvae of cnidarians (sea anemones and thimble jellyfish) and also seaweed dermatitis.

Climate can adversely affect the skin of indigenous people preferentially living in harsh rural terrains. Miliaria is common in infants due to heat. Lip biting and chewing (triggered by mucosal dryness) is common in young males [17]. Heat, humidity, and possibly hair structure predisposes to trichomycosis axillaris from *Corynebacteria* in young indigenous adults of both sexes. Proximal axillary (and rarely pubic hair) develop yellow, occasionally red and uncommonly black, concretions that may be associated with malodor and hair brittleness. Wood's lamp examination may fluoresce yellow or blue-white. Differentiation from lice and powder can also be made by demonstration of Gram-positive bacilli and by incubation on blood agar at 37 °C after immersion of hair in 70 % alcohol [17].

Nutrition

Urbanization, the dislocation of resettlement, and poor dietary awareness have led to increased obesity in indigenous compared with nonindigenous Australians. A study of rural indigenous children showed the prevalence of overweight children being 22.1 % and 20.7 % for girls and boys, respectively, with corresponding figures for obesity of 5.1 and 5.8 % [22]. Pseudoacanthosis nigricans is therefore common, presenting with velvety pigmentation of the nape of neck and axillae (Fig. 48.2). Skin tags may subsequently occur. Underlying conditions such as polycystic ovarian syndrome and diabetes (which is increasing in indigenous children in Australia and the USA) should also be considered [23].

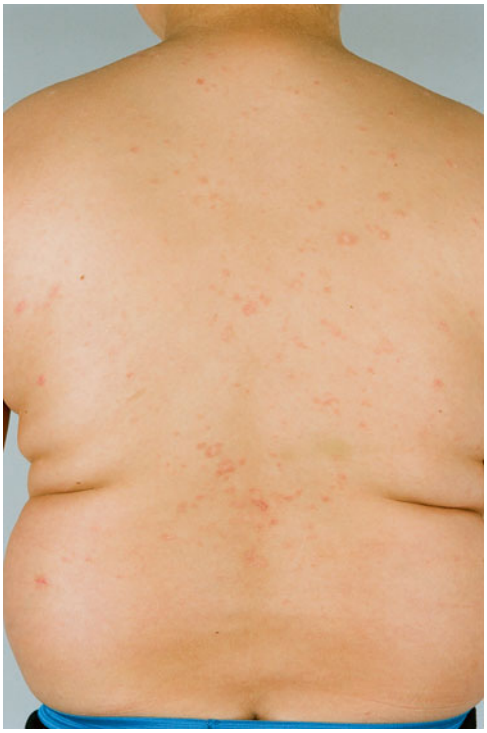

Fig 48.2 An 11 year old boy from south-eastern urban Australia with obesity, early pseudoacanthosis nigricans, severe combined immunodeficiency and pityriasis rosea, 9 years after stem cell transplant (Royal Children's Hospital, Melbourne)

Infection

Infectious diseases represent the overwhelming burden of skin morbidity in which indigenous children are overrepresented.

Scabies and Pyoderma

Epidemiology/Demographics

- **In some indigenous Australian communities, scabies prevalence is 30–50 % of children and that of pyoderma/impetigo is 10–70 %**
- **64 % of children presenting with scabies have concurrent bacterial infection**
- **The endemic, concurrent, recurrent, and complicated nature of infections have led to community-specific management protocols**

High rates of *Staphylococcus aureus* skin and soft tissue infections—and particularly methicillin-resistant *Staphylococcus aureus* (MRSA)—have been documented in indigenous people from Australia, Canada, USA, and New Zealand [24–30]. Increased rates of diabetes and renal disease may predispose to invasive staphylococcal disease. Scabies frequently coexists with and also predisposes to these bacterial skin infections.

Scabies has a prevalence of 30–50 % in some communities of Aboriginal Australian children and it underlies 70 % of pyogenic skin infections [31–33] (Fig. 48.3). Pyoderma/

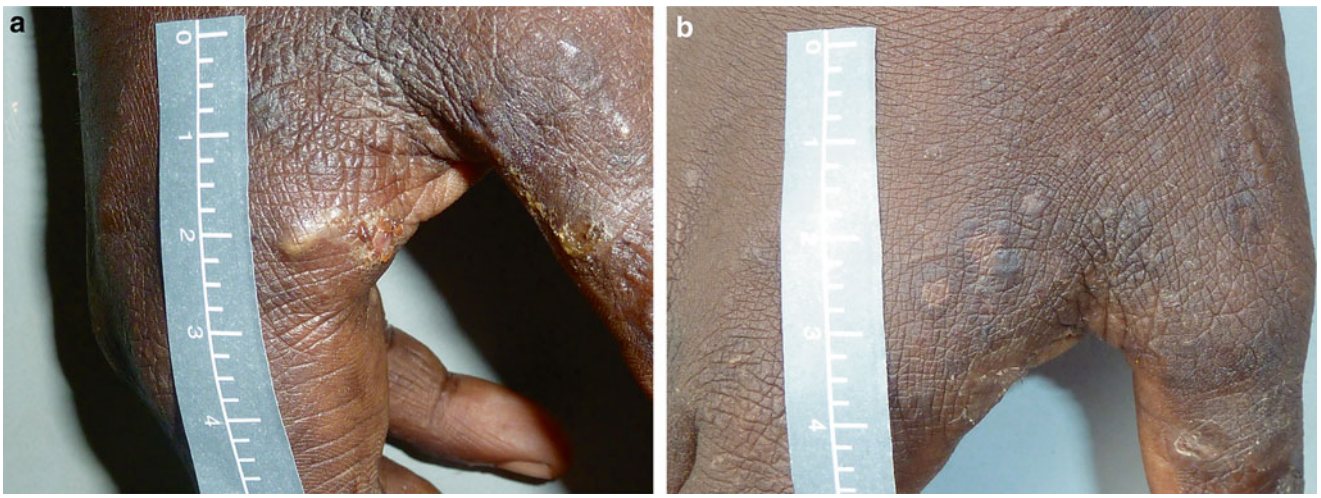

Fig. 48.3 Concurrent scabetic, *Streptococcus pyogenes* and *Staphylococcus aureus* infection, (**a**) before and (**b**) after treatment with cotrimoxazole twice-daily over 3 days in an 11 year old boy living in a 3 bedroom home with nine family members in Northern Australia (credit: Dr Asha Bowen)

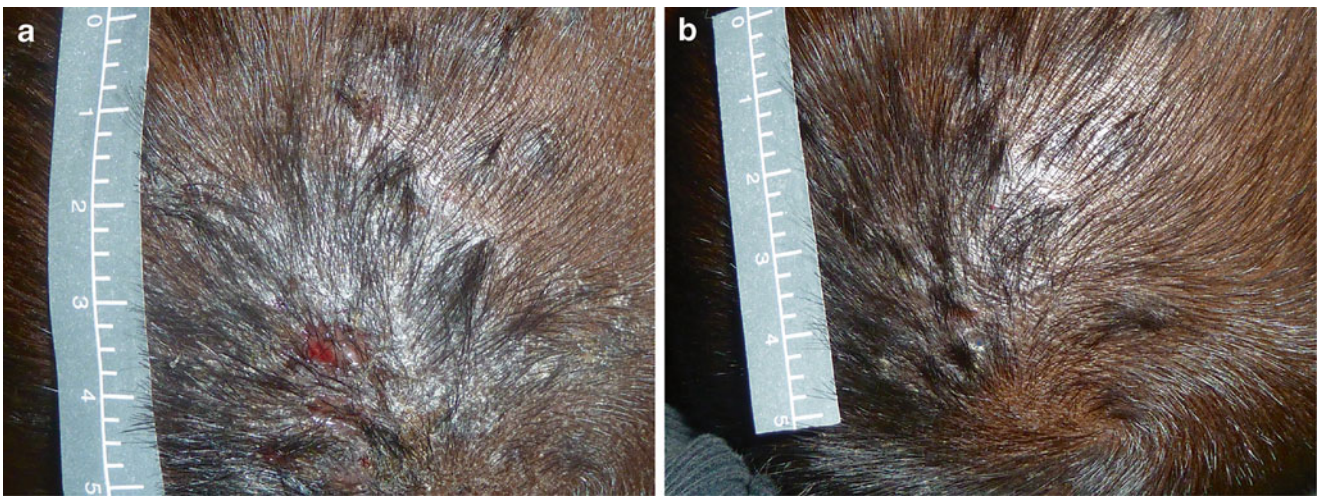

Fig. 48.4 (**a**) A scalp sore in a 2 year old girl living in a 4 bedroom house with 11 relatives in remote Northern Australia. Group C streptococcus and *Staphylococcus aureus* were identified. (**b**) After treatment with intramuscular benzathine penicillin G (credit: Dr Asha Bowen)

impetigo occurs in 10–70 % of Aboriginal children in remote communities [7, 31]. Group A *Streptococcus pyogenes* (GAS) is found in 80–93 % of the swabs for impetigo [7, 31]. Of note, whereas Group C and Group G *Streptococcus* can also cause similar skin and soft tissue infections and are more frequently isolated in the throat than are GAS, they are rarely identified in skin sores and usually then only together with GAS or *Staphylococcus aureus* [34] (Figs. 48.4 and 48.5). *Staphylococcus aureus* (including community-acquired MRSA) is increasing in incidence in more affluent urban areas, where *Staphylococcus aureus* prevalence now approximates GAS amongst indigenous Australians [35, 36].

Of children affected by scabies, 10 % develop scabies by 6 weeks of age, 50 % by 6 months, and 68 % by 1 year [7]. Similarly, 10 % of children with impetigo have been infected before 9 weeks of age [7]. The ubiquity of pyoderma in indigenous Australian communities previously raised the defined threshold of pyoderma treatment to 'six infected sores', but now treatment is recommended for all sores [37]. 64 % of children presenting with scabies have concurrent bacterial infection [7].

Clinical Presentation

- **Concurrence of scabies, streptococcal, and staphylococcal infection is common**
- **Atypical presentations of scabies may result from effects of tropical climate, immunosuppression, and chronic eczematization**
- **Group A *Streptococcus* is the most important cause of pyoderma and can lead to rheumatic fever, acute post-streptococcal glomerulonephritis (APSGN), and acute renal failure**

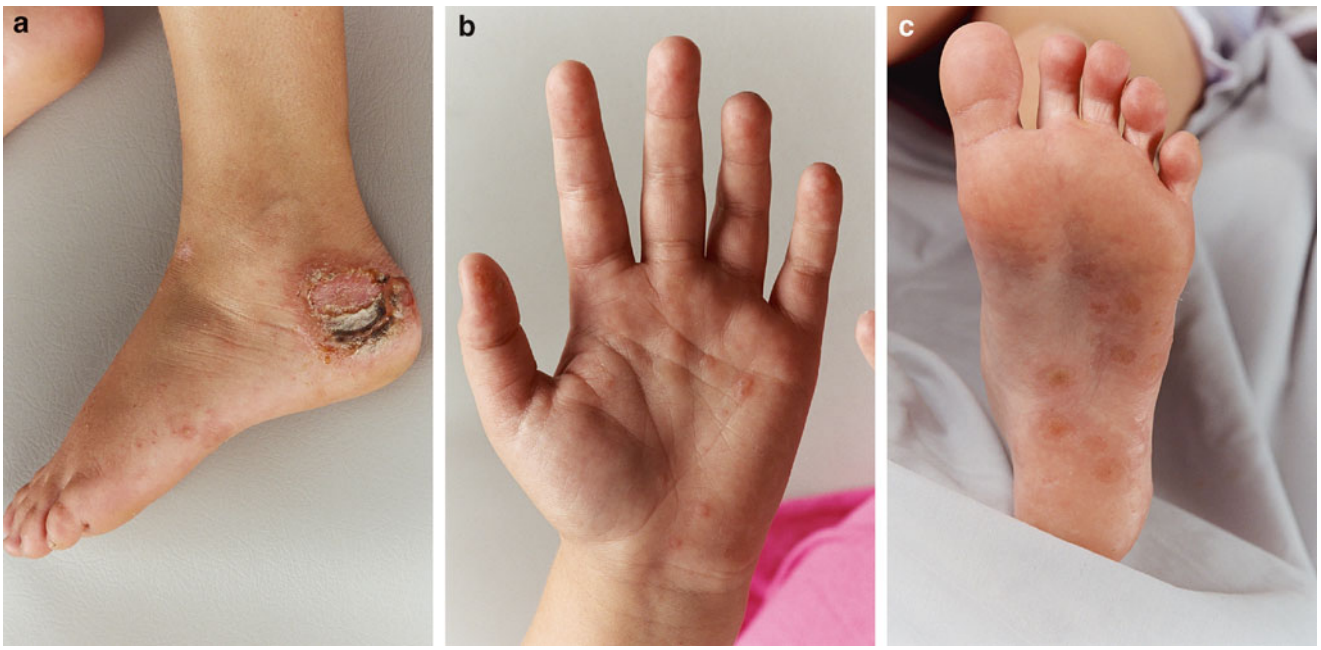

Fig. 48.5 (**a**) Group G Streptococcus and *Staph aureus* complicating tinea pedis in an 8 year old girl from urban south-east Australia, leading to an erythema multiforme like id response of (**b**) palms and (**c**) soles (Royal Children's Hospital, Melbourne)

Table 48.2 Treatment approach to scabies in indigenous Australian pediatric population (aged over 6 months)

First line therapy	5 % permethrin cream[a]	Apply to whole body overnight (sparing head, except in infants) and repeat application in 1 week
First line therapy	Treat family and close contacts	Utilize topical permethrin application as above
First line therapy	Treat clothing, bedding	Hot wash clothing and bedding or remove from body contact for >72 h
Second line therapy[b]	Oral ivermectin	200 μg/kg orally on two occasions, 1 week apart
Adjunctive therapy	Moderately potent corticosteroid	For post-scabetic pruritus which can persist for 2–8 weeks after eradication therapy

[a]Permethrin is not approved for children under 6 months of age, but has been used in infants >2 months in age. Crotamiton is first line treatment under 2 months of age. Alternative therapies are 5 % sulfur in white soft paraffin in patients under 2 months (10 % sulfur if >2 months of age) once daily for 3 days, or off label permethrin

[b]Ivermectin is first line therapy for crusted (Norwegian scabies) (200 μg/kg) and may require more frequent oral dosing and topical measures in severe cases

Scabies in indigenous children show typical scabetic burrows, pruritic papules, nodules, and a propensity for finger webs, flexor aspects of wrists, extensor aspects of elbows, periumbilical skin, buttocks, ankles, male genitalia, and female periareolar regions. Infants are often affected on the scalp, neck, axillae, and groin. However, burrows are often not visible for children living in tropical locations [38]. Furthermore, chronic eczematization and immunosuppression can lead to modified and atypical presentations. Crusted scabies is particularly seen in the immunosuppressed (due to primary immunodeficiency, immunosuppressive medications, and HIV or HTLV-1 infection) as well as in children with leprosy. Scabies acquired from animals with mange are rare and self-limiting due to host-specificity of mites. Fissuring predisposes to secondary infection with GAS and *S. aureus*, leading to impetigo and cellulitis. Head lice infestation and tinea also predispose to skin GAS infection in indigenous children [39].

Differential diagnoses include bites (midges, fleas, bedbugs), bacterial infections (folliculitis, impetigo), tinea, viral exanthems, and papular urticaria.

Treatment

Scabies

An overview of the management of scabies in indigenous Australian children is outlined in Table 48.2. Sensitivity in communicating with families is critical to optimize compliance, which is often poor in indigenous communities (Appendix). A 5 % permethrin is usually the first-line treatment, applied for 8–12 h overnight. A second 8–12 h application

after 1 or 2 weeks is particularly important for children [40]. Clothing and other possible fomites should be hot cycle washed or removed from body contact for >72 h. Concurrent treatment of household contacts is critical. Under 2 months of age, many practitioners use crotamiton or 5–10 % sulfur in paraffin, given the limited data on permethrin safety.

Ivermectin is an alternative treatment. Although licensed in France, it is not licensed for routine use in many countries (e.g. Australia, Canada, UK) and does not work on all stages of the mite cycle. Increasing in vitro resistance of *Sarcoptes scabiei* to permethrin and ivermectin has been reported [41, 42]. Clinical resistance should be particularly suspected if symptoms persist for several weeks in nonendemic areas. For crusted scabies, up to seven doses of ivermectin combined with topical therapy (permethrin and keratolytics) may be needed to eradicate the mites [43].

Streptococcus and *Staphylococcus*

Intramuscular benzathine penicillin is the treatment of choice in GAS endemic communities due to poor compliance with oral therapy and the imperative to treat GAS to prevent serious sequelae, despite potential staphylococcal antibiotic resistance. Given low rates of indigenous throat GAS carriage, pyoderma is considered responsible for most cases of rheumatic fever as well as APSGN in Aboriginal children. Oral phenoxymethylpenicillin can be considered if compliance is good. Antistaphylococcal beta-lactams are used in areas with staphylococcal predominance. Alternative oral regimens may be indicated in the case of antibiotic resistance and penicillin allergy (Fig. 48.6). Topical antibiotics are not used in endemic areas.

Boils (furuncles) are usually related to *S. aureus* and are best treated with incision and drainage. Flucloxacillin is used additionally in children (older adults with obesity and liver disease may have an increased risk of hepatotoxic complications). Nasal carriage is treated in chronic *S. aureus* carriers who experience recurrent infections, using 5–10 days of topical nasal mupirocin. Persistent reinfection will require determination of sensitivities and possibly repeated nasal mupirocin treatment or consideration of oral rifampicin. Bleach baths are an affordable and effective alternative therapy for persistent reinfection.

Cellulitis in Aboriginal communities is usually treated with procaine penicillin and elevation of the affected limb, although better *S. aureus* cover is required in urban communities [40]. Melioidosis and sporotrichosis also cause cellulitis and may require exclusion in atypical, refractory disease and particularly in adults with risk factors like diabetes, renal failure, and alcohol abuse.

Pyoderma prevention requires address of housing, education, and lifestyle problems. Introduction of swimming pools into communities has helped reduce infection rates, likely by reducing skin bacteria counts [44].

Efficacy of Treatment

A recent study in North Australia combined annual skin checks over a 3-year period with treatment of identified scabies cases and their household contacts with 5 % permethrin (or 10 % crotamiton for infants under 2 months) and treatment of impetigo (according to current guidelines) [37]. The study reported a 40 % drop in the rates of pyoderma especially in 3–14 year olds but no change in overall scabies prevalence, given poor treatment compliance.

In endemic communities, compliance with treatment is especially low amongst contacts, males, and in high scabies burden households [45]. Reasons cited for noncompliance

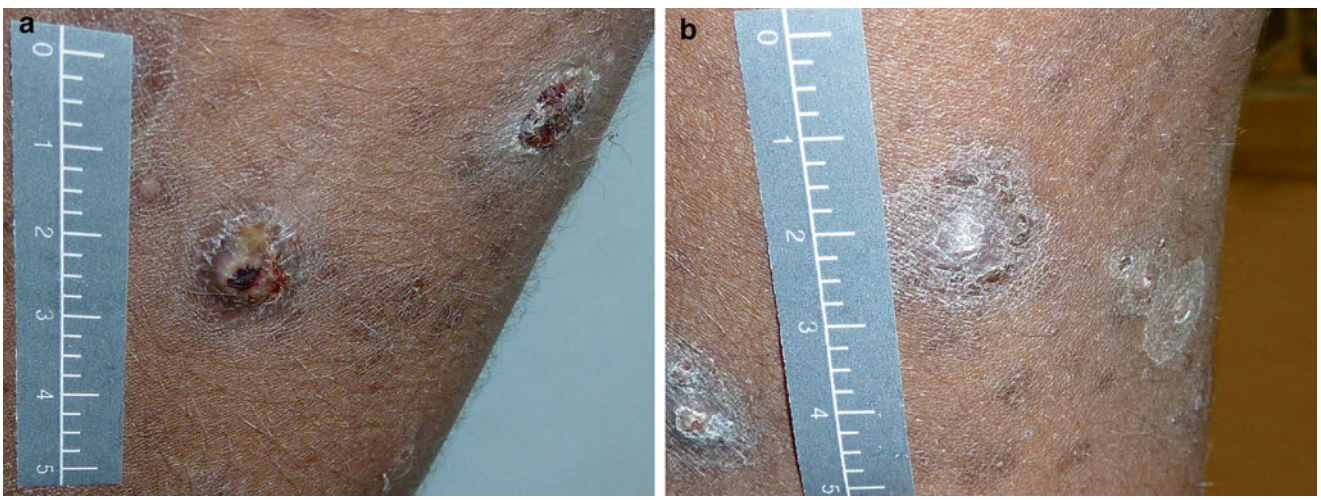

Fig. 48.6 Sores of an 8 year old girl from Central Australia infected with scabies, head lice, tinea and Strep pyogenes. She shared a two bedroom house with nine relatives. Treated with cotrimoxazole daily for 5 days and photographed (**a**) day 0 and (**b**) day 7 (credit: Dr Asha Bowen)

include perceptions that treatment is of low priority, a fixed belief that treatment is only necessary for the index case and that topical therapy is too uncomfortable to apply.

Other Infections

Mycobacterium

Increased prevalence of tuberculosis, relative to the nonindigenous population, has been identified in indigenous people from Canada, Australia, New Zealand, and USA [46]. Cutaneous tuberculosis (TB), however, is an uncommon presentation of extrapulmonary TB and may only be found in 1–2 % of cases. There are a wide variety of clinical presentations of cutaneous TB. The presentation in skin relates to whether skin involvement is due to exogenous infection (primary inoculation into skin) or endogenous infection (due to the spread of TB within an individual). Furthermore, the immune response to TB can precipitate skin changes known as tuberculids.

The crude incidence rate of TB in the Australian indigenous population is 6.6/100,000. This is seven times that of the nonindigenous population and there are even higher rates in rural regions (13-fold in the Northern Territory) [47]. Similar increased relative risk is found in the New Zealand and US indigenous population, whereas the indigenous population of Canada carry a 35.2-fold increased risk compared to their nonindigenous counterparts. Australian Aboriginal children also carry a higher risk than non-Aboriginal children, but the incidence is much lower than adults. This suggests that differing environmental exposures (overcrowded housing, prisons) may contribute to the overall increased risk in Aboriginal Australians.

Unlike TB, a recent study in the Northern Territory did not find increased atypical mycobacterial disease in Aboriginal groups [48]. In this study, all cases of atypical mycobacterial infection in Aboriginal children presented with lymphadenitis in children under 10 years of age. Risk factors for skin infection with *M. fortuitum*, *M. chelonae*, *M. abscessus*, *M. marinum* and *M. ulcerans* in indigenous adults include HIV, chronic lung disease, smoking and alcoholism. Whereas *M. scrofulaceum* was previously the main cause of non-TB pediatric lymphadenitis in Aboriginal children, mycobacterium avium complex now accounts for 50 % of cases. Surgical excision alone is usually successful. However, tuberculous lymphadenitis is six times more common than non-tuberculous lymphadenitis, so unless proven otherwise, treatment must be directed towards TB.

Mycobacterium ulcerans, sometimes termed 'Daintree ulcer' or 'Bairnsdale ulcer' in Australia, is endemic in some regions of Queensland and Southeastern Australia and can present as a firm, painless nodule which breaks down to form a painless necrotic ulcer. The incidence of infection is increasing in Australia, though this likely reflects improved diagnosis [49]. *M. ulcerans* is best treated with surgical excision, with consideration of antibiotic therapy (with rifampicin and amikacin) for extensive disease.

Leprosy is caused by the obligate intracellular pathogen *Mycobacterium leprae* and is transmitted through close contact. Leprosy is a chronic granulomatous condition that primarily affects skin, mucous membranes, peripheral nerves, eyes, and testes. In the majority of patients, hypoesthesia is the first sign of disease, particularly of the extremities. Leprosy was not endemic to Australia prior to European settlement; however, the introduction of the disease in the late 1800s caused an epidemic across Northern Australia. Prevalence in some Aboriginal communities was determined to be 10 % in the 1950s with an overall prevalence of 270 per 100,000 indigenous Australians [50]. By 1997 the prevalence had fallen to 4/100,000 and it is now rare in Australia. Fifty-four patients were reported with leprosy in Australia between 2005 and 2010; however, indigenous patients represented only a minority, with the majority of patients being migrants from leprosy-endemic countries [51, 52]. Indigenous patients do continue to present with leprosy to healthcare practitioners in rare instances and clinicians must remain alert to the disease [53].

Melioidosis

Melioidosis is caused by the Gram-negative bacterium *Burkholderia pseudomallei* and is endemic to Northern Australia and parts of South East Asia. Sporadic reports of disease have also come from Central and South America, the Middle East, and Africa. 80 % of Thai children have antibodies by age 4, and a 3-year-old Australian case has been reported [54]. Soil or surface water is the usual source, although animals can also be infected and transmit disease by contact. The incidence in indigenous Australians is 25.5/100,000, four times the average north Australian incidence [55]. Other risk factors include diabetes mellitus, renal disease, and alcoholism, thus most cases occur in adults. About 80 % of cases occur during the wet season. 50 % of patients present with pneumonia, 6 % with osteomyelitis, and 6 % with skin and soft tissue infection (furuncles, cellulitis). Genitourinary, neurological, and gastrointestinal systems can also be affected. Chronic cases can mimic tuberculosis. Mortality in one series of 47 cases (including adults) was 21 %. Treatment includes ceftazidime and meropenem and must be started early.

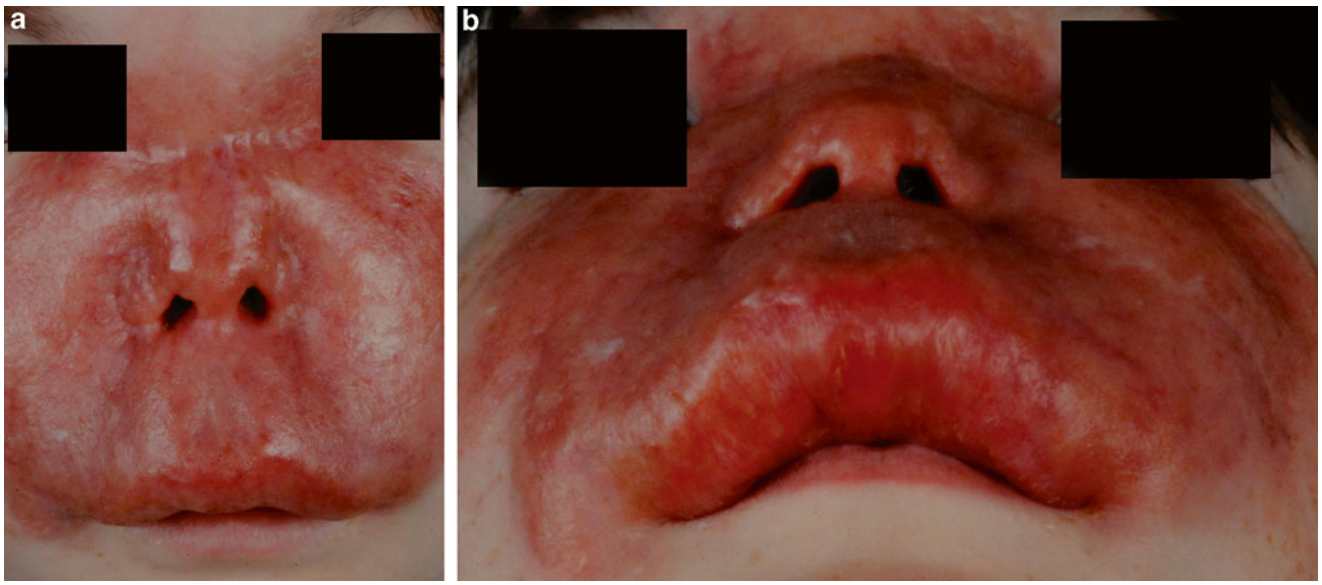

Fig. 48.7 A slowly progressive, granulomatous, midline facial plaque in a 5 year old Tasmanian boy. Amoebic trophozoites and cysts were only identified in a brain biopsy after developing granulomatous amoebic encephalitis (Royal Children's Hospital, Melbourne)

Free-Living Amoebae

Infection by *Balamuthia mandrillaris* is being increasingly reported. *B. mandrillaris*, a free-living amoeba, is found in soil whereas other free-living amoeba like *Acanthamoeba* and *Naegleria* are acquired mainly from water bodies like creeks and ponds. Although reported worldwide, children in rural communities and warmer climates are at particular risk [56]. High-risk subpopulations include Hispanics in the USA and children under 15 in Peru. The first reported Australian case was an 8-year-old indigenous boy from a rural community in Tasmania [57] (Fig. 48.7). The relative importance of genetic and recreational factors is unclear. The commonest skin presentation is a mid-facial, rubbery, nonulcerating plaque that may have a raised edge. Satellite lesions, as well as elbow, knee, chest and oral involvement have been described. Direct and hematogenous spread are possible, resulting in encephalitis within weeks or years. Differential diagnosis of the cutaneous plaque includes leishmaniasis, sporotrichosis, tuberculosis, Wegener's granulomatosis, sarcoidosis, granuloma faciale, NK-T cell lymphoma, and midline lethal granuloma.

Diagnosis may rely on histopathological identification, where poorly defined, noncaseating superficial and deep dermal tuberculoid granulomas are seen, often with perineural accentuation. Multinucleate giant cells, lymphocytes, and plasma cells are also evident. *Balamuthia* trophozoites measure 12 ± 60 μm in diameter with a round nucleus and large, dense nucleolus and are found in 2/3 of skin biopsies. They can be confused with macrophages histologically to the undiscerning eye. Immunohistochemical and immunofluorescent staining is highly sensitive and specific, but not readily available and PCR is not routinely available. Unlike other free-living amoebae, it does not grow on bacteria-coated agar plates. Serology (indirect immunofluorescence and ELISA) is not specific.

Prolonged, multidrug agent therapy is recommended; however, the outcome is often poor. Treatments include amphotericin B, imidazole, albendazole, macrolides, sulfadiazine, metronidazole, pentamidine, and isethionate. Addition of miltefosine has been reported to help survival.

Worms

Hookworm

Ancylostoma duodenale is the predominant cause of hookworm infection in Aboriginal Australian children, although similar disease follows infection by *Necator americanus* and the zoonotic species *A. caninum*, *A. braziliense*, and *A. ceylanicum* [58]. Acquisition follows cutaneous penetration by larvae and occasionally by fecal-oral spread. The prevalence of hookworm in Aboriginal children 5–14 years old in some communities has been estimated to be as high as 93 % [59]. It can cause iron deficiency anemia and hypersensitivity reactions. Ground itch (inflammation at the site of larval skin penetration) is characterized by itchy papules and erythema. Migration of the larvae under the skin results in cutaneous larva migrans which is characterized by red, edematous and serpiginous tracks, particularly on the feet, buttocks and abdomen. Eosinophilic enteritis, if present, is usually self-limiting.

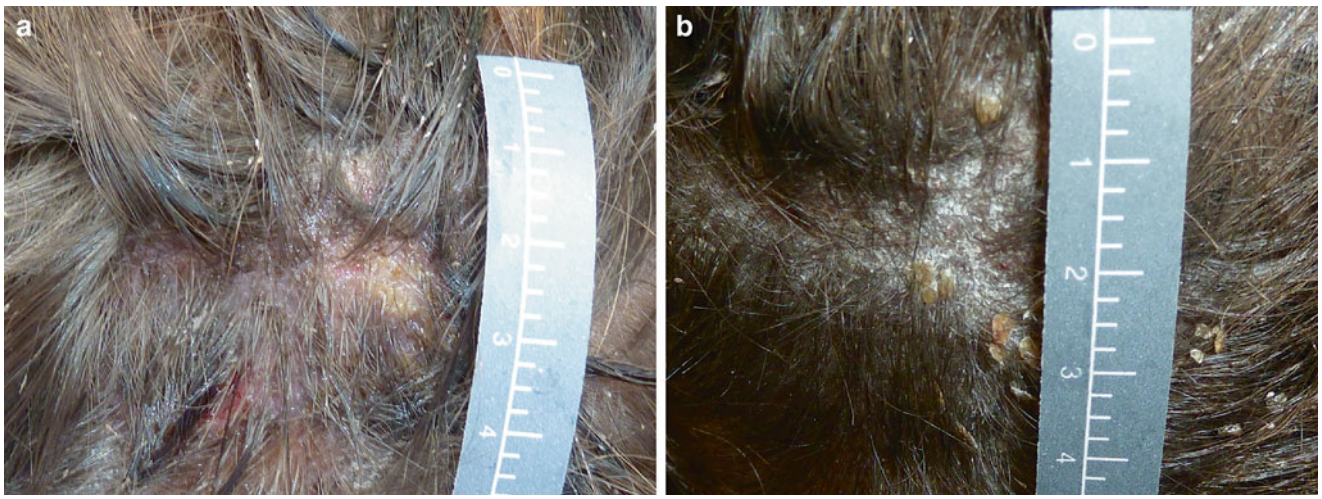

Fig. 48.8 Tinea capitis with secondary *Streptococcus pyogenes* and *Staphylococcus aureus* in a 6 year old girl from central Australia (**a**) before and (**b**) after treatment with cotrimoxazole twice-daily for 3 days. She shares a 3 bedroom house with 16 relatives

In high-risk areas, children 6 months to 12 years can be treated with albendazole as a single oral therapeutic dose every 4–6 months and this has reduced community prevalence [60]. Resistance of *A. duodenale* to pyrantel has been demonstrated, so alternative therapy may be preferred [61].

Strongyloides stercoralis

Prevalence of strongyloidiasis in indigenous communities is unclear, but using fecal microscopy, 15 % of members of one remote community showed *Strongyloides* parasites, as did 7 % of Indigenous children hospitalized for diarrhea in another study [62, 63]. Larvae penetrate the skin before migrating to the alveole, pharynx, and finally, the bowel. Larvae can autoinfect, when the rhabditiform larvae transform into filariform larvae with the passage of feces. Immunosuppression may result in hyperinfection and death.

Cutaneous features include recurrent urticaria and larva currens. There may also be abdominal pain, nausea, diarrhea, weight loss, hypokalemia, and pulmonary and neurological complications [63]. Eosinophilia is common, but may be absent in disseminated disease [60].

Diagnosis may be difficult to confirm. Stool microscopy has low sensitivity but is enhanced with stool concentration [64]. Agar plate culture requires viable larvae [60]. ELISA may help diagnosis and monitoring, but the time for seroconversion is unclear. *Strongyloides stercoralis* DNA detection in stool is sensitive and specific, but it does not differentiate viable from nonviable larvae [65].

Fungal Disease

In a 1977 study, tinea prevalence in Aboriginal children in North Australia 6–16 years of age was 10.6 % [66]. *Trichophyton tonsurans* and *T. violaceum* are the commonest causes of tinea capitis, although *T. rubrum* and an unusual variant of *M. canis* known as Maningrida type are also seen [67] (Fig. 48.8). Tinea corporis is usually caused by *T. rubrum*, and can include an unusual granular variant (Fig. 48.9). The same dermatophyte usually causes cases of onychomycosis, although only 25–36 % have positive cultures and microscopy and a further 31 % are positive on microscopy only [68]. Oral terbinafine shows much better results than both griseofulvin and topical treatments for tinea corporis, particularly given low compliance with the topical therapy [67].

Cryptococcus neoformans and *C. gatti* are overrepresented in the indigenous Australian population with rates of 8.5 per million and 10.4 per million respectively. These compare with rates of 4.4 and 0.7 cases per million respectively for nonindigenous people. It is found in bird excreta, dust, soil, and skin. Although *C. gatti* (associated with the *Eucalyptus camaldulensis* tree) is more common in Aboriginal Australians generally and often affects immunocompetent hosts, *C. neoformans* predominates in rural regions like the Northern Territory where it mainly affects immunocompromised people [67]. Although the main features are pulmonary disease and meningitis, it can also cause skin acneiform papules, pustules, nodules, abscesses, ulcers, warts, vegetating or infiltrated plaques, and panniculitis. 10–15 % of cases can have skin changes

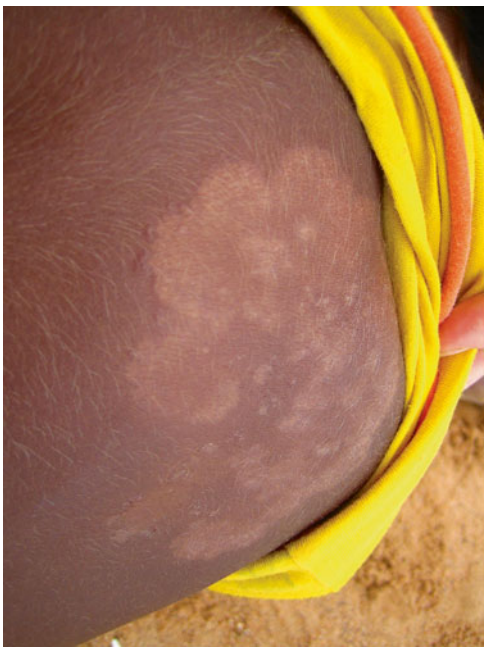

Fig. 48.9 Tinea corporis in a Central Australian boy (credit: Dr Claire Grills)

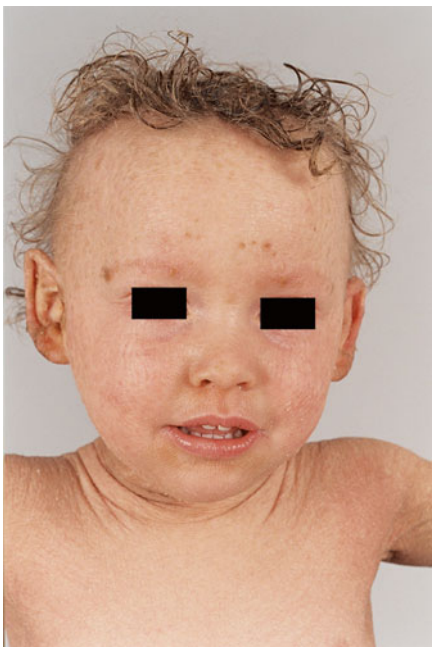

Fig. 48.10 Lamellar ichthyosis in a 2 year old indigenous boy (Royal Children's Hospital, Melbourne)

that may disseminate after 2–8 months, leading to fungaemia and multisystem organ involvement. Diagnosis is made by skin biopsy (histology, microscopy using PAS and India ink stains, and culture), by latex agglutination (serum, CSF, urine), and ELISA (blood, CSF). Skin disease responds to oral fluconazole, or itraconazole.

Aboriginal children are also at higher risk for developing histoplasmosis and fungal keratitis. Other diseases overrepresented in Aboriginal Australians include syphilis, donovanosis, and other sexually transmitted infections.

Ongoing Research

While the burden of infectious skin disease in the indigenous Australian pediatric population is well described, little is known about the burden of noninfectious skin disease (Fig. 48.10). In the general indigenous Australian population, relatively low rates of psoriasis, type 1 hypersensitivity disorders, and skin malignancy are found, compared with high rates of lupus erythematosus (Table 48.3) [21]. It is likely that prevalence in the pediatric population reflects that of the adult population for these conditions, but this has not been specifically examined in the literature.

Table 48.3 Prevalence of select non-infectious conditions in general indigenous Australian population compared with non-Indigenous Australian population [21]

Condition	Prevalence compared with non-indigenous
Psoriasis	Less prevalent/rare[a]
Eczematous conditions	Unknown/conflicting studies
Type 1 hypersensitivity disorders	Less prevalent
Systemic lupus erythematosus	More prevalent
Discoid lupus erythematosus	More prevalent[a]
Melanoma	Less prevalent/rare
Non-melanoma skin cancer	Less prevalent[a]
Vitamin D deficiency	More prevalent
Kava dermopathy	Likely more prevalent

[a]Indicates prevalence based upon anecdotal evidence only

In Australia, despite the National Health and Medical Research Council (NHMRC) allocating 5 % of its annual research budget to indigenous health, there are significant holes in our knowledge of indigenous pediatric disease [69]. Research into the three-quarters of all young indigenous Australians who live in urban and regional areas is particularly sparse compared to those in remote communities [70, 71]. Furthermore, recent research into indigenous health in Australia has been criticized as lacking interventional studies and focusing on observational research [72].

Summation/Conclusion

An understanding of the burden of skin disease affecting indigenous children in USA, Canada, New Zealand, and Australia is essential to all healthcare practitioners seeking to address disparities in the health and wellbeing afflicting these children. Infectious skin diseases, particularly *Staphylococcus aureus*, Group A *Streptococcus* infections, and scabies, represent a particularly major burden of skin disease in indigenous children and physicians must account for multiple concurrent pathologies.

Appendix

Table 48.4 A general approach to a consultation with an indigenous Australian patient

Understand the importance of land and place	Land or 'country' is at the core of Aboriginal spirituality, law, identity, and culture. Taking interest in where a patient may originate from can be helpful in establishing rapport
Acknowledge the role of family	Indigenous families may not operate according to a Western 'nuclear' family model. Care of children and decisions on treatments often involve the extended family and the patient's community
Recognize language barriers	For many indigenous patients and families, particularly in more remote settings, English will be a second (or third) language. Avoid medical jargon and during the consultation assess for their understanding of what you have said and offer the chance to ask questions
Respect their silence	An indigenous person's silence may suggest they are reflecting upon what has been said, considering their response or translating what may not be their first language. Allow pauses and avoid interrupting
Be patient with your time	Some consultations with indigenous patients may be more complex and more time may need to be invested to ensure effective communication and understanding
Avoid eye contact	Some indigenous patients' and their families may find direct eye contact confronting or aggressive. Adopt nonthreatening body language and sit at an angle to the patient rather than front-on
Be holistic	Recognize that health problems can often relate to a variety of other circumstances that may include poor housing, education, family dysfunction, substance abuse, etc. Simple medical interventions may be unsuccessful if this is not recognized and a holistic approach is not taken
Seek concordance rather than compliance	Adherence to therapy in indigenous patients is often poor if there is a lack of understanding, if they are not convinced or if they are marginalized in the decision making process. Concordance refers to the process of discussion between doctor and patient, and participation by both in reaching an agreement about a management plan
Utilize aboriginal health/liaison workers	They often have a broader understanding of the patient and their family's personal circumstances and can assist with communication

[a]The nature of a consultation with an indigenous patient and their family will vary according to a range of factors. The above will not apply to all patients in all circumstances but rather provides an overview of strategies for clinicians to consider using on a patient-by-patient basis [72–75]

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Skin Cancer Epidemic in American Hispanic and Latino Patients

49

Bertha Baum and Ana Margarita Duarte

Abstract

The 2012 US Census states that Hispanics or Latinos comprise almost 17 % of the US population (Humes KR, Jones NA, Ramirez RR. Overview of race and Hispanic Origin: 2010. Washington, DC: U.S. Census Bureau; 2011. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf). And this is envisioned to continue to grow in size in the next 20 years. The prediction made by the US Census Bureau is that by the year 2050, 50 % of the US population will be comprised of minorities including Hispanics, Asians, and African Americans (Census 2000. US Dept of Commerce Economics and Statistics Administration, US Census Bureau; 2002. http://www.census.gov/prod/2002pubs/c2kprof00-us.pdf. Accessed 7 Mar 2008). Because of this growth and influx of Hispanics in the United States, now, more than ever, it is pivotal to raise awareness of skin cancer in people of color.

Keywords

Skin cancer epidemic • American Hispanic • Latino • Melanin

Background/Introduction

The 2012 US Census states that Hispanics or Latinos comprise almost 17 % of the US population [1]. And this is envisioned to continue to grow in size in the next 20 years. The prediction made by the US Census Bureau is that by the year 2050, 50 % of the US population will be comprised of minorities including Hispanics, Asians, and African Americans [2]. Because of this growth and influx of Hispanics in the United States, now, more than ever, it is pivotal to raise awareness of skin cancer in people of color.

As recently published by Jaimes et al. [3], the term Hispanic and/or Latino lacks consensus and may be interpreted in different ways. It is important to understand that these terms are used interchangeably, and they may refer to the ethnicity, origin, or race of patients. With the differences within the Hispanic/Latino spectrum, in terms of races based on location and the range of skin types, should bring a much larger debate that will not be discussed in this chapter. The terms will be used considering both as one large entity, the Hispanic/Latino group.

It has been believed that melanin helps protect the skin against effects of the sun such as skin cancers and premature aging [4]. In African American and Hispanic skin, melanin may provide a sun protection factor (SPF) around 13.4, compared to 3.4 in white skin [5]. This might explain why skin cancer is the most common type of malignancy in people with light skin color and low amounts of melanin [6]. The well-known carcinogenic consequences of the ultraviolet light caused by the sun and also tanning beds/lamps have been in many cases the main cause of skin cancer in Caucasian Americans.

As it is well recorded in the literature that Caucasians are the primary victims of skin cancer, there is a lack of understanding that everyone, regardless of skin color, can be

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susceptible to it. Unfortunately, many patients and even some physicians are under the impression that non-Caucasian people are immune to skin cancer or protected from it. And it is believed that this and other reasons can explain why people of color are diagnosed with skin cancer at later stages [7]. This delay may signify that skin cancers are often advanced and potentially fatal in Hispanic patients, whereas most skin cancers are curable if diagnosed and treated in a timely manner.

Melanoma is the most lethal form of skin cancer, accounting for about 75 % of all skin cancer deaths [8]. Generally, incidence rates increase with age, peak after age 40, and are greater in men than in women [9]. However, these trends do not reflect what is typically seen in minority ethnic groups, where incidence rates are lower [10]. In addition, for some groups, relative disease-specific survival also is lower compared with European-Americans. Melanomas in minority populations also tend to appear in atypical locations and are of unclear etiology [11]. Among fair-skinned Hispanics, it has been shown that the trunk and legs are the most common locations for melanomas, while the feet (Fig. 49.1) are the most common location in dark-skinned Hispanics [5].

The incidence of cutaneous melanoma has been growing over the past decades [12]. In the past 20 years in the USA the rate has doubled, giving melanoma the sixth place of the most common cancers in the USA and obviously a leading cause of death [13]. This has been accounted to many reasons, one of them is awareness, and therefore earlier diagnosis in general. To improve our understanding of the causes of melanoma arising in ethnic minority population, future research efforts are needed. In addition, the general lack of knowledge of this skin cancer among minority populations and the presentation of advanced disease in most of the cases highlights the need for educational programs for both patients and health care professionals [5, 10].

Although uncommon, melanoma is associated with poor survival characteristics among Hispanics compared with non-Hispanic patients [14]. In recent research also a focus on low socioeconomic status has been associated with poor survival among patients with melanoma, but it is not known whether this is because of the status itself or because of treatment differences in those groups [15]. Mainly due to delayed diagnoses and advanced stage at disease presentation, the 5-year mortality rates of non-Caucasians who have melanoma are higher than those of their Caucasian counterparts [7].

The most common forms of skin cancer are the non-melanoma skin cancers (NMSC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Both of these have been linked to intermittent and/or chronic sun exposure [16]. The correlation between UV light and basal cell carcinoma in darker skin types explains the relatively higher incidence of this malignancy among darker-skinned populations living in warmer climates, such as Hispanics residing in New Mexico and Arizona [17]. BCCs rarely metastasize. However, one study showed that when Hispanic patients develop BCCs they are more likely to have multiple lesions (Fig. 49.2) either at the time of presentation or in ensuing years [18]. Risk factors other than chronic sun exposure for BCC in minority populations include previous radiation therapy, very fair skin, or skin depigmentation i.e. albinism, immune suppressive drugs, trauma or any chronic scarring processes, arsenic exposure, solid organ transplantation, a personal or family history, and/or a genetic skin conditions i.e. Nevoid BCC syndrome [19].

SCC is the most common skin malignancy in African Americans and the second most common skin cancer among Hispanics [20]. The major difference is that UV light is not the primary risk factor for the development of SCC (Fig. 49.3) in people with skin of color [21]. Skin conditions that result

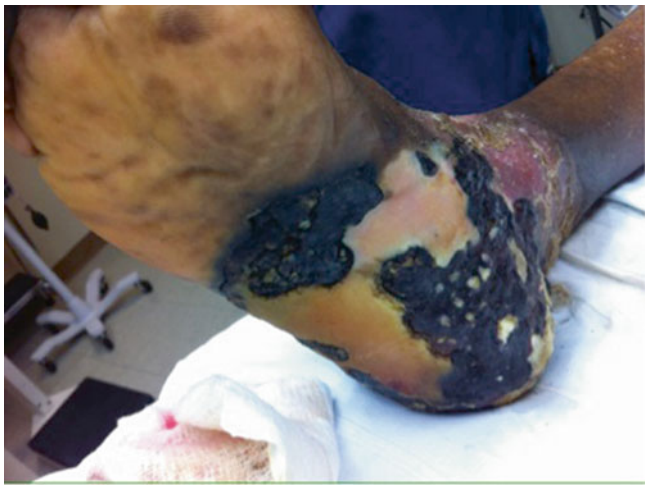

Fig. 49.1 Advanced stage melanoma in a Hispanic patient

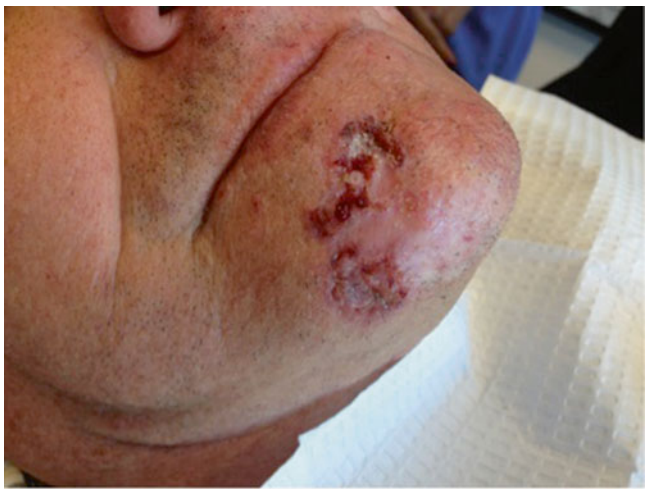

Fig. 49.2 Multiple BCC's on the chin of this Hispanic patient

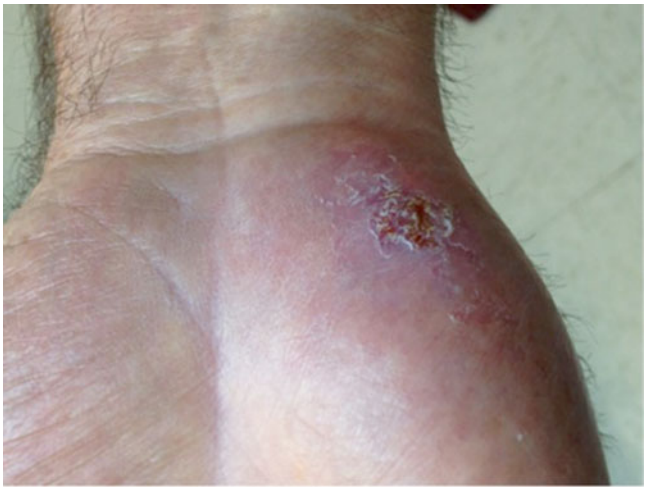

Fig. 49.3 SCC on the volar surface of the right hand on this Hispanic patient, treated for 20 years as eczema

in scarring, including burn scars and nonhealing skin ulcerations are the main risk factors, along with radiation therapy. Also patients with chronic inflammatory diseases such as hidradenitis suppurativa, discoid lupus, hypertrophic lichen planus, leprosy have a higher risk of developing SCC [22]. The SCCs that Hispanic patients develop tend to have a higher tendency to lead to metastasis and death [5]. One reason for this is, again, later detection and treatment.

Among Hispanic individuals, BCC is six times more likely than SCC [23]. In contrast, SCC is the most common skin cancer in the black population [24]. Melanoma is the third most common skin cancer among all racial/ethnic populations. Although melanoma is predominant among white men compared with white women, the incidence of melanoma in men and women is similar in black, Hispanic, and Asian/Pacific Islander populations [25]. The clinical features of skin cancers (such as appearance, type, and anatomic site) also vary according to race/ethnicity, as it will be further discussed.

Epidemiology/Demographics

The overall incidence of cancer in Latin America is estimated to be 163 cases per 100,000 people, which is a much lower rate than in the USA or Europe [26]. However, the proportion of people who die from cancer in Latin America is almost twice than in the USA, with around 13 deaths for every 22 cases of cancer in Latin America, compared to around 13 deaths for every 37 cases of cancer the USA, and approximately 13 deaths for every 30 cases of cancer in Europe [27]. Researchers estimate that by 2030, almost two million cases of cancer will be diagnosed in Latin America and the Caribbean, with more than one million deaths from cancer predicted to occur annually.

Latin America and the Hispanic population is facing an alarming increase in cancer rates, and unless urgent action is taken to prevent cancers, improve health care systems and facilities, access to vital medical care, and treatment of poor people, the USA will be overwhelmed by this inevitable epidemic. Many have stated that patients are diagnosed when the disease is at a late stage, making it obviously much harder to treat and more likely to have poor outcomes. Also the socioeconomic status in some of the Latin American countries and populations can be poor, rural, or indigenous communities, which provides little access to cancer treatments; a problem exacerbated by low, and highly inequitable, health investment in most Latin American countries.

Hispanics have the lowest rates of dermatology visits, many don't ever visit the dermatologist when they are young [28]. Because skin cancer prevention and screening practices historically have been lower among Hispanics, Blacks, and Asians, and given the changing demographics in the United States, interventions that are tailored to each of these groups will be needed [29]. Campaigns to educate the public should be targeted to educate people of all skin types, including the possibility of developing skin cancers in areas not exposed to the sun [30], since sunlight is not the most important cause of developing most of skin cancer in people of color [31].

Other important risk factors are imperative to recognize, because the focus is placed on the white- and light-skinned individuals based on the susceptibility to the UV radiation. Many risk factors include personal or family history of melanoma, evolving or changing nevi, new nevi after a certain age (most likely after 35 years of age), history of blistering sun burns at young age, immunosuppression, and fitzpatrick types I and II. Because some of these risk factors do not apply to the minority population, more understanding is needed in this subject and further research is an urgent matter.

Recent studies have demonstrated that the photoprotection from melanin in individuals with skin of color is only partial [32]. They have shown an association between melanoma and UV radiation in non-whites [15]. However, some studies have shown the data is inconclusive [33]. One important factor to consider is that other sun-protected sites such as palmar, plantar, and mucosal surfaces have been linked to melanoma, demonstrating there are others causative factors. And this, as mentioned previously, should be a key point when focusing on prevention campaigns.

The top four states for detailed Hispanic origin groups with a national population size of one million or more in 2010 US Census Bureau [1] are California, Texas, New York, and Florida. More than 60 % of the Mexican origin population in the United States resided in California and Texas. About 41 % of the Puerto Rican population lived in two

states, New York and Florida. More than 60 % of all Cubans lived in Florida, while Dominicans were highly concentrated in New York. About 32 % of people from Guatemalan and 50 % of Salvadoran population were concentrated in California. Demonstrating campaigns should be targeted to certain areas in order to capture a larger Hispanic audience.

Clinical Presentation

- Hispanics present with more advanced, thicker tumors, and poorer prognosis compared to white patients
- There is a lack of skin cancer education among Hispanics
- Hispanic patients are not engaging as much in preventive activities.

The correlation between number of nevi and age is stronger in Hispanics and non-Hispanic whites than in any other ethnic/racial group [34]. Hispanics present the highest rates of thick melanoma at time of diagnosis, being twice as likely to present with regional or distant metastasis [35]. Also another important and different factor is that more than 50 % of BCCs in patients with skin of color are pigmented compared to 6 % in white individuals [36].

Hispanic individuals tend to present with more advanced, thicker tumors, and thus tend to have a poorer prognosis with higher mortality compared to white patients. Bradford et al. [11] reported that the acral lentiginous melanoma 5- and 10-year melanoma-specific survival rates were 80.3 % and 67.5 %, respectively, which were less than the overall rates for cutaneous malignant melanomas (91.3 % and 87.5 %, respectively). The acral lentiginous melanoma 5- and 10-year melanoma-specific survival rates were highest in non-Hispanic white individuals (82.6 % and 69.4 %, respectively), intermediate in black individuals (77.2 % and 71.5 %, respectively), and lowest in Hispanic white individuals (72.8 % and 57.3 %, respectively) and Asian/Pacific Islanders (70.2 % and 54.1 %, respectively). In a retrospective review of case reports from the Florida Cancer Data System, Hu et al. [37] showed that higher-stage melanomas were more common among Hispanic (26 %) and black patients (52 %) compared to white patients (16 %). This can be suggestive of the socioeconomic lack of access to health care, while other causative factors cannot be ignored and may explain the discrepancy in survival rates among ethnic groups.

There are very little data and studies that approach the topic of melanoma among Hispanics mainly because there is scarcity of cases in the USA and there are limitations on the ethnicity information in cancer registries. With recent reports [38] stating only 23.9 % of Hispanics' visit the dermatologists not only can we explain the delay in diagnosis but also the small number of cases to date for research purposes. Most published studies on skin cancer incidence and mortality describe data for whites only.

Based on a recent study [39], factors associated with ever conducting a skin self-exam and a full body exam by a dermatologist included older age, English acculturation, higher risk factors for melanoma, more frequent sunscreen use, sunbathing, job-related sun exposure, higher perceived skin cancer risk, and doctor recommendations among others. In this particular study, the rates reported of ever conducting a skin self-exam or having a full body exam were 17.6 % and 9.2 %, respectively. These values reveal the lack of skin cancer education among Hispanics and the need for more investigation in this area, also to be able to understand why Hispanic patients are not engaging as much in preventive activities.

Treatment

Treatment of NMSC (nonmelanoma skin cancer) includes Mohs surgery, surgical excision, cryosurgery, electrodesiccation and curettage (ED&C), and creams (fluorouracil/imiquimod) as well as photodynamic therapy among others. Certain factors such as size of lesion, location, and type determine the treatment options for each patient. For the metastatic types, other treatments such as radiation and oral medications have been used. For melanoma skin cancer many more variables come into play to make a decision in terms of treatment. Most of the times, an oncologist is involved when metastasis or larger tumors are found. The treatment options of localized cutaneous melanoma include a wide local excision and sometimes even amputations, depending on the site involved. Chemotherapy, radiation, IL-2, and experimental cancer vaccines are among other treatment choices.

According to the National Cancer Institute, melanoma staging is based on the thickness of the tumor (Breslow thickness), tumor ulceration, spread to lymph nodes, or spread to other parts of the body [40]. There are five stages, Stage 0, I, II, III, IV. Stage 0 being melanoma in situ, while Stage III includes lymph node involvement, and Stage IV includes distant spread to other parts of the body, including lung, liver, brain, bone, soft tissue, or the gastrointestinal system [1].

Although the incidence of melanoma is lower in Hispanics than in non-Hispanic white patients, the stage at time of diagnosis is often more advanced in Hispanic patients [41]. There is limited data regarding melanoma stage at time of diagnosis among Hispanic Americans. A study by Hu et al. [37] evaluated 41,072 cases of melanoma from 1990 to 2004 with known race/ethnicity and stage information that were reported to the Florida Cancer Data System (FCDS). It revealed that at presentation, both white Hispanics and black patients had significantly more advanced staged melanoma at diagnosis, 18 % and 26 % respectively, in comparison to 12 % of non-Hispanic white patients [15].

Another study analyzed 81 melanoma cases between 1970 and 1986 from the New Mexico Melanoma Registry and New Mexico Tumor Registry [42]. This study found that 36 % of Hispanics had more advanced stages of melanoma with 2 mm or thicker in depth, while only 16 % of non-Hispanic white patients had lesions at an advanced stage. Melanoma is highly curable if detected at early stages. According to the American Cancer Society, the 5- and 10-year survival rates are 91 % and 89 %, respectively. The 5-year survival rate drops to 62 % for regional disease and 15 % for distant stage disease [43].

Other factors affecting the disparity of melanoma stage at diagnosis may include socioeconomic status, education on skin cancer awareness, and cultural and social values. According to Ward et al. [43], residents of poorer counties have 13 % higher death rates from cancer in men and 3 % higher in women when compared to wealthier counties. Often Hispanic patients and even physicians in the medical community have a low index of suspicion of skin cancers in these ethnic populations. This frequently leads to a delay in diagnosis and subsequent advanced presentation and poorer prognosis. This further emphasizes the need for more skin cancer awareness programs and education on the importance of sun protection even in ethnicities with lower index of suspicion for skin cancer.

Primary skin cancer prevention efforts among US Hispanics and campaigns should be starting, this way preventing the delay on the NMSC and melanoma diagnosis. Promoting (1) the use of sunscreen or sunblock, (2) the use of sun-protective clothing and/or hats, and (3) shade-seeking behavior should be a norm at all dermatology office visits and also a review on the patients' physical exams. It is important to understand that improvements are needed in primary skin cancer prevention practiced by Hispanics. Preventive measures should be taught and hopefully practiced more often by the Hispanic populations. Primary care providers need to promote the importance of full body exams and they should be part of the patients' yearly well physical check up.

Prognosis

The 5-year survival rates for melanoma is 77.1 % for white Hispanic males, 86.8 % for white Hispanic females, 86.5 % for non-Hispanic males, and 92.2 % for non-Hispanic white females [42]. Although there is a difference in numbers of cancer deaths among the ethnic groups, there is a lack of studies on ethnic disparities with respect to melanoma within groups. Improved secondary prevention will help the prognosis among Hispanics since melanoma prognosis is directly proportional to stage at diagnosis.

The number of basal cell and squamous cell skin cancers (nonmelanoma skin cancers or NMSC) is difficult to estimate because these cases are not required to be reported to cancer registries [44]. Some suggest that 3.5 millions are diagnosed each year in the USA [45] and an estimated 3,170 deaths from NMSCs will occur in the USA in 2013 according to the skin cancer foundation [46].

Most patients with primary cutaneous SCC have a very good prognosis [47]. Conversely, those with metastatic disease have a poor long-term prognosis. Patients with regional lymphadenopathy have a less than 20 % 10-year survival rate, and patients with distant metastases have a less than 10 % 10-year survival rate [47]. When metastasis does occur, it mainly involves the regional lymph nodes. Distant sites, including the lungs, liver, brain, skin, and bone, are less often affected [47]. Also Patients with SCC are at risk for developing other malignancies such as cancers of the respiratory organs, buccal cavity, pharynx, small intestines (in men), non-Hodgkin's lymphoma, and leukemia. Five-year cure rates after treatment for primary SCC were 96.9 % with Mohs Micrographic Surgery (MMS) compared with 92.1 % with all other forms of treatment.

Five-year recurrence rates after treatment of primary BCC are 1 % for MMS, 7.5 % for cryotherapy, 7.7 % for ED&C, 8.7 % for radiation therapy, and 10.1 % for surgical excision [48]. The main goal in the treatment of BCC should be complete removal of the malignancy with the highest cure rate and least cosmetic disfigurement or functional impairment.

In general it is imperative to note that the earlier the diagnosis in melanoma or NMSC, the better outcome. Preventive campaigns should try to understand and target the reasons for the lack of measures used in a timely fashion by the Hispanic populations in the USA. And focus should be placed specifically in the high Hispanic populated and influx areas.

Ongoing Research

Future studies and interventions need to account for the difference in sociocultural backgrounds, degree of acculturation, and occupation among US Hispanics, which can help predict the amount of awareness that needs to be raised and also the focus on future prevention campaigns. Also some studies should be done directly based on health care providers to fill in the gap when it comes to Hispanic patients and skin cancer.

Recent studies have examined predictors of skin cancer-related behaviors in bicultural Hispanics (defined as people that are Hispanic but live outside of a Latin country or are raised in another country). As expected, results suggested that bicultural Hispanics seek shade and wear sun-protective clothing less often than Spanish-acculturated Hispanics but more often than English-acculturated Hispanics. No relationship was found with sunscreen use in this study [49].

The higher costs for the thicker melanoma management should promote an approach to earlier detection programs among Hispanics. Insufficient prevention programs exist, promoting education and awareness about signs and symptoms of skin cancer, focusing on the early visit and the difference in consequences based on the delay of seeking help.

Based on the Hispanic growth rate increasing at a three-fold in comparison to the US population, a strong need and changes should be made to provide health care and research for a better outcome in skin cancer survival in the Hispanic population. The focus should be place on prevention methods for early detection and treatment.

Socioeconomic factors may impede access to care, but it has been proven that Hispanics even with good health care access delay the visits to the primary care doctor or dermatologist. Hispanics and their providers need to gather a more detailed family history, sun-exposure history, and self-exam history to determine which patient would need closer monitoring based on risk factors.

Summation/Conclusion

Primary care doctors should encourage patients to visit the dermatologists once a year and to ask their specialists such as their gynecologist, dentist, and ophthalmologist to look for abnormal pigmentation during routine exams. To reduce the burden of skin cancer, prevention methods should be encouraged, such as monthly self-examinations, daily use of SPF 30 or greater sunscreen, sunglasses with UV-absorbing lenses, and avoiding tanning booths [50].

In addition, recommendations for clinicians to promote the prevention of skin cancer in skin of color needs to be made, including closely monitoring changing pigmented lesions on the palms and soles and hyperkeratotic or poorly healing ulcers in immunosuppressed patients [24]. Also, Hispanic patients with scarring conditions and with other risk factors should be monitored closely.

The use of sunscreen campaigns, emphasizing on the importance of the application of the sunscreen, on the selection of the correct type of sunscreen and the continuous application process, should be a must on hispanic communities. A review of other protective UV gear and general tips should be aimed towards this population. Awareness of the power of self-examination and education on how often they should be performed and what at the patient needs to look for.

Also prevention should start in the pediatric population and more emphasis has to be made on younger patients and their parents. In order to teach the Hispanic population and the general population a better understanding of the cause and effect that continuous sun exposure in the first 15 years has on skin cancer development later in life, dermatologists and general practitioners need to transmit this message. Campaigns about sunscreen application and UV protected clothing and caps need to be geared toward the pediatric population. The introduction of sunscreen with colors and glitter can make the protection fun and elicit more compliance with kids helping parents with continuous applications. In sports activities, physical education classes, summer camps, and other outdoor activities there should be availability of sunscreen and shade on a continuous basis.

As seen on recent studies, like Pipitone et al. [51], in which they compared Hispanics and non-Hispanics who possessed similar access to health care, it was reported that the Hispanic cohort performed fewer skin self-examinations. Echoed in the adolescent population, Hispanic white high school students were 60 % less likely than non-Hispanic white students to have heard of skin self-examinations and 70 % less likely to have ever been told to perform one [52]. These studies demonstrate the target audience for these campaigns, obviously Hispanic, will fall into all socioeconomic categories and should be tailored with that in mind.

The significant rise on advanced melanoma diagnoses in Hispanics than in non-Hispanic whites [53]. In this recent study, significantly higher proportion of advanced (regional and distant) melanomas were diagnosed in non-Hispanic blacks (19.1 %) and Hispanics (17.1 %) than in non-Hispanic whites (8.7 %) ($P<0.001$), demonstrating once again the growing need to educate patients and health care providers [53].

The economic consequences of melanoma-related deaths in the USA have productivity losses and it is very important to understand in order to evaluate the interventions for skin cancer prevention. In a recent study, it was suggested that the total productivity losses attributable to melanoma-related mortality were approximately 66.9 billion [54].

Our job as health care providers, and dermatologists, is to educate in order to prevent disease. In the case of the skin cancer epidemic in American Hispanic and Latino patients, there is a big battle that awaits us, but acknowledging the problem puts us a step ahead. If we continue to create the right campaigns and target accordingly the Hispanic population, earlier skin cancer detection will be part of the Hispanic culture. In this chapter and recent studies, we propose different ways of prevention and lines of research to hopefully win the battle and stop this epidemic before the population growth becomes larger and harder to control.

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