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Update on melanocytic nevi in children

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Abstract A new or changing melanocytic nevus in a child or adolescent often leads to concern in parents and physicians. To avoid undue alarm and unnecessary procedures, dermatologists should be aware of the natural history and clinical spectrum of nevi in pediatric patients, as well as findings that are potentially worrisome in this age group. This review provides an update on melanocytic nevi in children, focusing on their dynamic evolution over time, molecular insights into nevogenesis, and phenotypic markers for increased risk of melanoma in adolescence and adulthood. Special considerations for Spitz nevi and nevi located in particular sites (eg, scalp, acral, genital) are highlighted. Current understanding of the risks associated with congenital melanocytic nevi of different sizes and strategies for the management of children with numerous acquired nevi, Spitz nevi, and congenital nevi are also discussed.

Epidemiology and overview

Melanocytic nevi are an almost ubiquitous finding in pediatric patients.[1] By the end of the first decade of life, nevus counts reach a mean of 15 to more than 30 in white children and 5 to 10 in those of African, Asian, or Native American heritage.[2,3] The number of nevi typically peaks in the third decade, subsequently decreasing with age. In stark contrast, melanoma is extremely rare during childhood but becomes progressively more common with age, with a peak in the seventh decade of life.[4] Approximately 0.5% of melanomas occur in individuals younger than 20 years of age, with less than 0.05% developing in patients younger than 10 years of age.[4,5] Melanomas in children tend to be amelanotic and nodular, presenting as a rapidly growing "bump" that may mimic a pyogenic granuloma, keloid, or wart rather than a changing nevus.[6–8]

Although the frequency of prepubertal melanoma has remained stable, the rising incidence of melanoma in adolescents and adults over the past few decades has led to heightened awareness among both the public and physicians. Concern about a new or changing melanocytic nevus in a child often prompts parents and pediatricians to request evaluation by a dermatologist. To avoid undue alarm and unnecessary procedures, it is crucial for dermatologists to be aware of the natural history and clinical spectrum of nevi in children, as well as findings that are potentially worrisome in pediatric patients.[9–12]

This review provides an update on the clinical and dermatoscopic features of melanocytic nevi in children, focusing on their dynamic evolution over time and phenotypic markers (eg, numerous acquired nevi) for increased risk of melanoma in adolescence and adulthood. Special considerations for Spitz nevi and nevi located in particular sites (eg, scalp, acral, genital) are highlighted. Current understanding of the molecular basis of nevogenesis (Table 1), risks associated with congenital melanocytic nevi

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Table 1 Molecular pathways of nevogenesis

Gene with somatic mutation or rearrangement	Typical type(s) of melanocytic nevi (~% of lesions)	Other melanocytic lesions (~% of lesions)	Other cutaneous manifestations (~% of lesions)
BRAF^{V600E}[a]	Banal acquired (70–90) Atypical acquired (50–80) Congenital: Small (70–85) Medium (30) Large (5–10)	Cutaneous melanoma (esp. superficial spreading; 50–60)	
NRAS[a]	Congenital [Q61 K/R] Medium (70) Large/giant (85–95) + their satellites CMN-type large SpLN [Q61 H] (>90)	CNS lesions in NCM[b] Proliferative nodules in CMN Cutaneous melanoma (10–30)[b]	Nevus sebaceus (5) Epidermal nevi (5)
HRAS[a]	Spitz[c] (15–20) ASN[c] (10–15) Conventional and PPK-associated SpLN (>90)		Nevus sebaceus (95) Epidermal nevi (30) Woolly hair nevi
Kinase fusions of *ROS1, NTRK1, ALK, BRAF,* or *RET*	Spitz (50–60) ASN (50–60)	Spitzoid melanoma (40)	
BRAF[a] plus loss of *BAP1*[d]	Atypical spitzoid (esp. if intradermal; 25)	Uveal melanoma (50)	
GNAQ[a]*/GNA11*[a]	Blue (70-85/10)	Nevus of Ota (10/5) Malignant blue nevus (50/20) Uveal melanoma (30-40/40-50)	Port wine stains (90/?)

ASN, atypical spitzoid neoplasm; *BAP1*, BRCA-associated protein-1/ubiquitin carboxy-terminal hydrolase; *CMN,* congenital melanocytic nevus; *GNAQ/11,* G protein α-subunit Q or 11; *NCM,* neurocutaneous melanocytosis; *PPK,* phacomatosis pigmentokeratotica; *SpLN,* speckled lentiginous nevus.

[a] Activating mutation.

[b] Same mutation as in the associated nevus.

[c] *HRAS* copy number increases may be found alone or together with an *HRAS* mutation.

[d] In addition, heterozygous *germline* inactivating mutations underlie an autosomal dominant tumor predisposition syndrome (see text).

(CMN) of different sizes, and strategies for the management of children with numerous acquired nevi, Spitz nevi, and CMN are also discussed.

Acquired nevi in childhood and adolescence: growing moles in growing patients

During the past decade, multiple studies have emphasized that melanocytic nevi in children and adolescents have morphologic features and behavior that differ from nevi in adults. On dermatoscopic evaluation, a globular pattern predominates among acquired nevi in children as well as CMN, especially for lesions located on the head, neck, and upper part of the trunk.[13–17] In contrast, a reticular pattern is more common for acquired nevi that develop in adulthood or are located on the extremities. Children with Fitzpatrick phototypes III to VI also tend to have smaller nevi with a reticular pattern.[15,18,19]

Two pathways for the evolution of melanocytic nevi—(1) the formation of soft, skin-colored papules (intradermal nevi) and (2) a gradual fading away via atrophy or fibrosis—were described more than a half century ago by Stegmaier.[20] More recently, the hypothesis of separate pathways of nevus development has been refined to include dermatoscopic and even molecular characteristics.[15,21,22] It has been suggested that a "constitutional" pathway gives rise to nevi with a globular pattern, which tend to have predominantly dermal growth and/or large junctional nests, an underlying *BRAF*^{V600E} activating mutation, and possible derivation from neural crest–derived melanocyte precursors that reach the dermis of the head/neck and dorsal aspect of the trunk early in embryogenesis.[21,22] These nevi tend to have congenital or childhood onset and evolve via Stegmaier's first pathway. The "acquired" pathway results in nevi with a reticular pattern that have predominantly junctional growth (often lentiginous) and favor the extremities. Such nevi most often develop during adulthood and involute via Stegmaier's second pathway.

Although a changing nevus in an adult may raise suspicion for melanoma, growth (especially enlargement of newer lesions and increases in elevation) and other types of evolution are normal parts of the natural history of melanocytic nevi during childhood and adolescence.[12] One group[23] followed the nevi on the faces and necks of 110 adolescents over a 4-year period and noted a dynamic process of nevus turnover, with a more than 50% net increase

in nevus number and complete regression of approximately 15% of nevi. Most new nevi were small and flat, and there was a general tendency for existing flat nevi to either become elevated or disappear (ie, to follow Stegmaier's first or second pathway). Another study of 366 11-year-old children found that the median nevus count on the back increased by two over a 3-year period, with at least one nevus disappearing in 28% of the children.[24] There have been other reports of clinically atypical nevi in children regressing or developing into nevi with banal features.[25]

Evolution of pigmented lesions has been highlighted as a key component of the ABCDE (**a**symmetry, **b**order irregularity, **c**olor variability, **d**iameter >6 mm, **e**volving) criteria that raise clinical suspicion for melanoma.[26] Enlargement, which is often characterized by a peripheral rim of brown globules on dermatoscopy, occurs in less than 5% of banal-appearing nevi in adults and is often associated with histologic atypia[27]; however, up to 60% of nevi in children enlarge over a period of approximately 1 year, and this is not associated with histologic atypia.[27] Similarly, a study that used short-term sequential dermatoscopic imaging of pigmented lesions with a minor clinical suspicion of melanoma found that changes were significantly more common in children and adolescents (24%) than in young to middle-aged adults (15%), but the changing nevi were nearly twice as likely to have histologic evidence of atypia in adults (63%) than in children and adolescents (35%).[28] A recent analysis of more than 20,000 melanocytic lesions excised from Italian children and adolescents over a 20-year period found that 87% of the 38 melanomas were in the 15- to 19-year age group, with no melanomas in children younger than 10 years. The overall ratio of 594 nevi to 1 melanoma was 20-fold higher than that reported in adults.[29] These findings have led to the recommendation that a change in a nevus should not be used as the sole criterion for its excision in pediatric patients.[11,12,29] Recognizing this important difference between management of nevi in children and adults helps to avoid confusion, misplaced worry, and needless procedures.

Environmental and genetic factors in nevus development

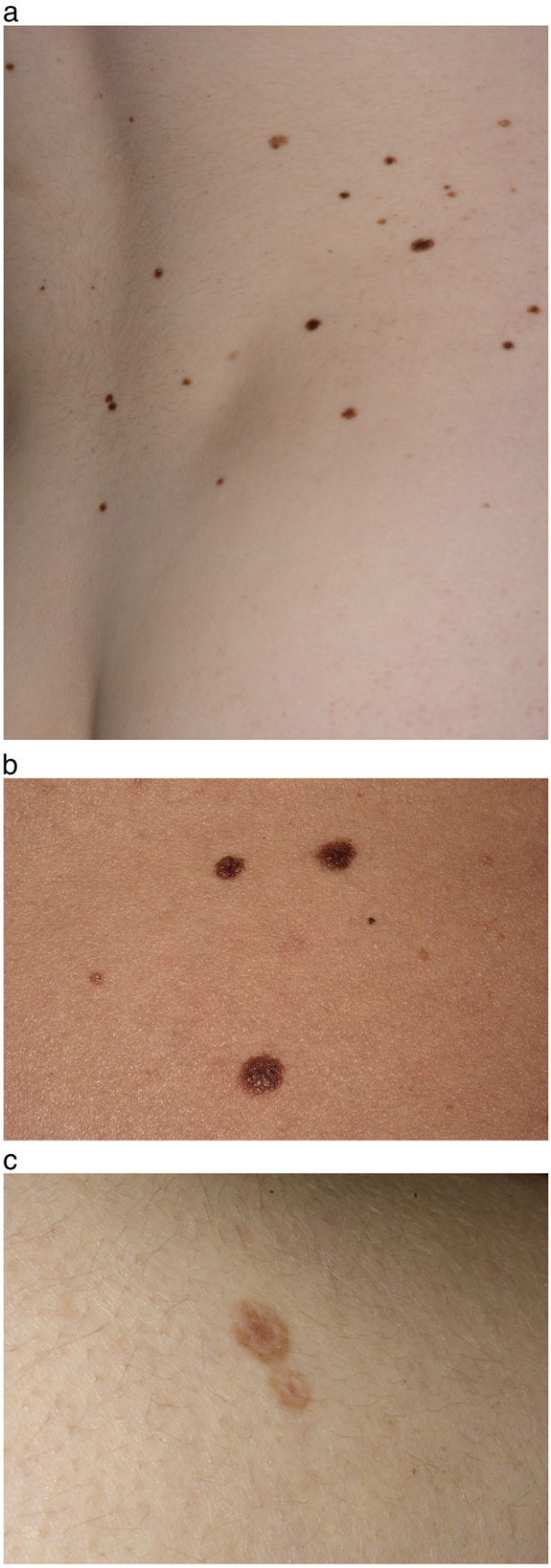
Sun exposure, especially when intense and intermittent, represents the primary environmental influence on the number and location of nevi that develop during childhood as well as later risk of melanoma.[30] White children living in a tropical climate tend to develop a higher peak nevus number at an earlier age (eg, mean peak of ~50 nevi at age 15 years) than those residing in a temperate location (eg, mean peak of ~25 nevi at age 25 years). Sunscreen use can be protective against nevus development if combined with a reasonable approach to sun exposure.[31] In a randomized controlled study, school-aged children who were supplied with and instructed to use a broad-spectrum sunscreen developed significantly fewer new nevi (particularly on the trunk) over a 3-year period than controls.[32,33] Inverse relationships between nevus count and wearing sunscreen and/or sun-protective clothing (eg, swim shirts) have also been documented in cross-sectional and cohort studies.[34,35] Surprisingly, some retrospective studies have found a positive correlation between sunscreen use in children and an increased number of nevi. It has been postulated that this results from sunscreen allowing increased sun exposure (a potential confounder that is difficult to quantify retrospectively) while providing an incomplete barrier to ultraviolet radiation.[31]

Hereditary factors in nevus development include pigmentary phenotype and genetic predisposition to "moliness." Children with lightly pigmented skin overall have higher nevus counts than those with darker complexions, with the exception of relatively few nevi in individuals with extremely fair skin that does not tan, especially when accompanied by red hair (the "red hair phenotype").[1,36] The highest number of nevi is found in children with Fitzpatrick skin type II and dark hair.[37] Pigmentary phenotype can also influence the distribution of nevi. For example, children with darkly pigmented skin have a relative predisposition to develop nevi on the palms and soles, a phenomenon that is not related to sun exposure.[38]

Based on the results of twin studies, it is estimated that more than half of variation in nevus density in adolescents is attributable to genetic factors not accounted for by pigmentary phenotype.[39] Several genes have been associated with nevus number and pattern.[40–43] Interestingly, a particular polymorphism in the interferon regulatory factor 4 gene *(IRF4)* has age-specific effects on nevus count, leading to higher numbers of flat nevi but lower numbers of raised/globular nevi in adolescents and lower numbers of all nevi in adults. Polymorphisms in other genes have been linked to an increased frequency of globular nevi *(TERT)* or decreased frequency of reticular nevi (*CDKN1B*, *MTAP*, and *PARP1*).[43]

Managing the "moley" child

Nevus phenotype manifests gradually during the first decade of life, with the predisposition to a high nevus count generally becoming apparent by 11 or 12 years of age.[44] Atypical nevi usually begin to appear around puberty and continue to develop during adulthood.[45] They represent benign acquired melanocytic nevi that share, usually to a lesser degree, some of the clinical features of melanoma (ie, **a**symmetry, **b**order irregularities/fuzziness, **c**olor variegation, and **d**iameter >6 mm). An increased total number of nevi is the best predictor of the presence of clinically atypical nevi, although adolescents occasionally have numerous nevi that all have uniform pigmentation and regular borders.



Having a large number of acquired nevi (eg, >50) and the presence of clinically atypical nevi each represents a marker of increased risk for the development of melanoma, and patients with either trait should be followed with periodic total body skin examinations beginning around puberty.[46,47] The risk of melanoma increases further for "moley" adolescents who have a family history of melanoma, a history of excessive sun exposure, lightly pigmented skin with a tendency to burn, and/or red hair.[48,49] The vast majority of acquired nevi (banal or atypical) themselves remain benign, however, with the lifetime risk of any particular mole transforming into melanoma estimated to be approximately 1 in 10,000.[50] Because more than half of cutaneous melanomas arise *de novo*, there is clearly no benefit to prophylactic removal of nevi.

Individual "moley" children tend to develop nevi with a characteristic clinical appearance, such as solid brown, solid pink, "fried egg"–like, tan centrally with a brown rim ("eclipse"), or even with an eccentric focus of hyperpigmentation.[51–53] This results in a predominant type of nevus, or "signature nevus"[52,54] (Figure 1). In addition, many individuals tend to develop melanocytic nevi with a specific dermatoscopic pattern.[55] Multiple halo nevi, which are associated with an increased risk of nonsegmental vitiligo, can also represent a form of signature nevi in children and adolescents.[52] A recent study reported that the interval between stage I/II (depigmented ring/fading nevus) and IV (repigmentation) may be a decade or more.[56] Recognition of a patient's signature nevus facilitates identification of the "ugly duckling"—a nevus that has different characteristics from their other nevi—that should be regarded with suspicion.[57] For example, the most concerning lesion in a teenage girl with multiple large fried-egg nevi on the back may be a small brown-black nevus with irregular borders on the leg.

Dermatoscopic monitoring and baseline close-up photographs of nevi can prove helpful in avoiding unnecessary surgery. The author and others do not recommend the removal of nevi with a goal of confirming the presence of architectural disorder histologically[58]; rather, a biopsy is indicated when the differential diagnosis for a lesion includes early melanoma. When performing a biopsy, partial sampling should be avoided unless the lesion is large and in a cosmetically sensitive area.

Site-related considerations for nevi in children

Melanocytic nevi in certain anatomic locations (eg, the scalp, genital area, and hands/feet) have traditionally led to

Fig. 1 Signature nevi in "moley" children and adolescents. a, Multiple nevi on the lower back, many with a "fried-egg" appearance. b, Several solid brown nevi with a mammillated surface. c, Cockade (targetoid nevi).

increased concern among parents and physicians. Underlying factors for this heightened alarm have included differences in the clinical appearance of the lesions, challenges in monitoring, and a higher likelihood of atypical histologic findings.[59] However, recent evidence has accumulated that nevi in these "special sites" in children and adolescents do not exhibit worrisome behavior, and better delineation of location-specific dermatoscopic features has aided in their clinical management.

Scalp nevi

The development of scalp nevi during childhood can serve as an early indicator of a "moley" individual, potentially heralding the eventual development of numerous and/or atypical nevi. In a population-based study of 8- to 9-year-old Swedish children (n = 1069), 7% had at least one scalp nevus, the presence of which was associated with an almost twofold higher total number of nevi than children without scalp nevi (median 14 versus 8, $P < .001$).[36] Nevi arising on the scalp or buttock during childhood have also been noted to represent an early clue to the diagnosis of atypical mole syndrome in those at risk due to their family history.[49,60]

Acquired scalp nevi in children and adolescents are most commonly found in the parietal area or on the vertex and often reach a size of more than 6 mm.[61–63] In addition to solid brown or pink lesions, eclipse (tan center with stellate brown rim; Figure 2) and cockade (targetoid) nevi are often seen on the scalp and may have a particular association with a higher overall nevus count.[62–65] The majority of scalp nevi display perifollicular hypopigmentation, a banal finding that can lead to a scalloped border or variegated pigmentation.[62]

Despite their role as a harbinger of future moliness, scalp nevi themselves are characterized by a tendency to involute over time. A process of gradual lightening and regression has been observed for various types of scalp nevi, ranging from eclipse lesions to medium and large CMN (see later).[65,66] Although nevi in this "special site" are more likely to display atypical histologic features, this is not associated with problematic clinical behavior.[67] As a result, several authors have emphasized that, in the absence of a superimposed suspicious finding, two-tone (eg, eclipse) or large scalp nevi can be followed clinically and do not need to be biopsied.[62,63,65,68]

Genital nevi

Little is known about pediatric genital nevi, which often cause more angst in parents and physicians than nevi in other locations. A recent retrospective study of 1159 consecutive patients evaluated for melanocytic nevi in my pediatric dermatology practice found a 3.5% prevalence of genital nevi, which were not associated with a higher total number of nevi or a family history of melanoma.[69] The genital nevi

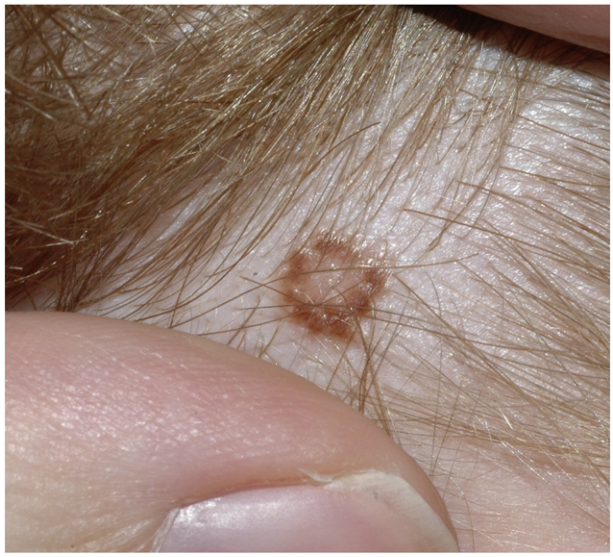


Fig. 2 Eclipse nevus on the scalp with a tan center and stellate brown rim.

tended to arise before age 2 years, have a globular dermatoscopic pattern, and follow a benign course (eg, evolving into more elevated, soft papules with a papillomatous surface). Biopsy or prophylactic excision of genital nevi in children is unnecessary in the absence of worrisome features. Of note, genital nevi on a background of lichen sclerosus have a particular tendency to develop clinical (eg, variegated brown-black pigmentation, irregular borders) and histologic features that mimic melanoma, so care should be taken to avoid misdiagnosis and inappropriately aggressive treatment of these benign lesions.[70]

Acral nevi and longitudinal melanonychia

Nevi located on the palms and soles are typically brown to dark brown in color. They often have linear streaks of darker pigmentation that reflect the prominent skin markings in these sites. In a recent Japanese study, dermatoscopic evaluation of acquired acral nevi in children and adolescents was more likely to show the "peas-in-a-pod" (parallel furrow plus crista dotted; also characteristic of acral CMN) or fibrillar pattern than in adults, but the parallel furrow pattern alone was most prevalent in both age groups.[71] Although acquired acral nevi with an atypical dermatoscopic the pattern that are more than 7 mm are viewed with suspicion,[72] larger size is not itself a red flag for congenital acral nevi.[73]

Acral nevi or lentigines that involve the nail matrix can present as longitudinal melanonychia, a tan, brown, or black streak caused by increased melanin deposition in the nail plate. In darkly pigmented individuals, such streaks are commonly seen on multiple nails due to increased melanin production by normal nail matrix melanocytes. Isolated bands of longitudinal melanonychia that develop in

childhood are usually benign,[74] often resulting from a junctional nevus of the nail matrix.[75] Gradual fading over time associated with the development of "dots along lines" was recently described in 8 of 15 Japanese children with longitudinal melanonychia followed over a 2-year period.[76] In adults, single bands that are very dark, wide ($\geq$6 mm), composed of irregular lines (in color, width, and spacing) on dermatoscopic evaluation, or associated with nail dystrophy or extension of pigmentation beyond the nail fold generally warrant biopsy of the nail matrix to exclude melanoma. In contrast, these findings often occur in association with benign lesions in children.[75] Histologic differentiation between *in situ* melanoma and benign melanocytic hyperplasia of the nail matrix is also difficult in children because normal parameters for melanocytes in this region have only been assessed in adults.[75] Further studies are therefore needed to develop guidelines for appropriate management of longitudinal melanonychia in pediatric patients.

Spitz nevi

Insights into the natural history of Spitz nevi

A Spitz (spindle and epithelioid cell) nevus is a distinct type of benign melanocytic neoplasm that most commonly develops in children. In several large series, approximately 50% to 75% of patients with lesions diagnosed histologically as Spitz nevi were younger than 20 years of age.[77–80] A Spitz nevus classically presents as a solitary pink, red, or brown papule, most often on the face (especially in young children) or lower extremity (Figure 3). Initial growth tends to be rapid, which can be alarming to parents and physicians alike. The surface may be smooth or verrucous, and lesions are commonly misdiagnosed as a wart, pyogenic granuloma, dermatofibroma, or juvenile xanthogranuloma.[81,82]

Dermatoscopy has emerged as an extremely useful tool in the recognition and longitudinal evaluation of Spitz nevi.[83–85] Pigmented Spitz nevi (including Reed nevi) often exhibit a characteristic symmetric starburst pattern composed of central dark, homogeneous pigmentation surrounded by peripheral streaks (radial streaming, pseudopods) or tiered globules.[83,84] Multiple studies using dermatoscopy to assess the natural history of pigmented Spitz nevi in children have reported that these lesions have a tendency to develop a reticular or homogenous pattern and/or regress over a period of months to years.[85,86] Nonpigmented Spitz nevi commonly display dermatoscopic features such as dotted vessels and a negative (white) network. The latter is thought to reflect elongated rete ridges and tends to be more symmetric than the relatively heterogeneous negative networks occasionally seen in melanomas.[83,87,88] Recently, a large study of nonpigmented as well as pigmented lesions with clinical and dermatoscopic features characteristic of Spitz nevi in children and young adults (mean age = 10 years) found that 80% (51/64 nevi) underwent involution over a mean follow-up period of 25 months.[86]

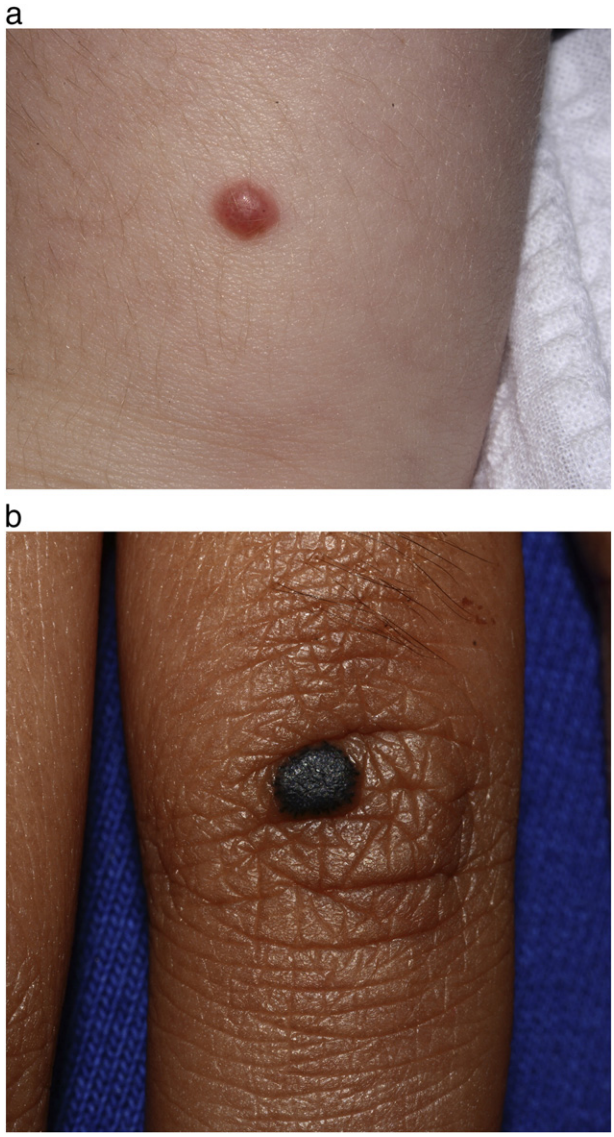


Fig. 3 Spitz nevi in young children. a, Pink-red, dome-shaped papule on the forearm. b, Brown-black papule with a starburst pattern that was highlighted by dermatoscopy.

New approaches to the management of Spitz nevi in children

Although they are benign neoplasms, Spitz nevi sometimes have histopathologic features that overlap with those of melanoma. This has led to controversies regarding appropriate strategies for the diagnosis and treatment of this type of nevus. Children are much more likely to develop Spitz nevi than melanomas, whereas the converse is true for adults.[89,90] As

discussed for other types of nevi (see earlier), the age of the patient represents an important consideration in the management of a skin lesion suspected to be a Spitz nevus.[82,83,91]

In a 2010 survey,[82] 175 pediatric dermatologists from the United States and around the world shared their collective experiences with a total of approximately 20,000 Spitz nevi, with a mean of approximately 10 Spitz nevi seen yearly per respondent. Ninety-six percent of the respondents and 100% (76/76) of those with an academic practice composed primarily of children believed that typical Spitz nevi are benign,[82] compared with only 74% (279/376) of respondents in a similar 2001 survey of primarily general dermatologists.[92] Eighty percent of the pediatric dermatologists used dermatoscopy and 96% avoided partial biopsies of Spitz nevi. In children with a suspected Spitz nevus, clinical follow-up was chosen by 49% of respondents for a small, stable nonpigmented lesion and by 30% for a pigmented lesion with a typical starburst pattern dermatoscopically.[82] Forty-seven percent of respondents had observed involution of Spitz nevi. No deaths had resulted from the approximately 10,000 Spitz nevi and atypical spitzoid neoplasms seen by the 91 respondents with academic or hospital-based practices.[82]

The ability to diagnose and monitor Spitz nevi dermatoscopically has led to new approaches to their management. Several groups have endorsed the option of longitudinal follow-up for Spitz nevi with classic clinical and dermatoscopic features in children younger than 12 years of age, with evaluation every 3 to 6 months until stabilization occurs and less frequently thereafter.[82,85,91,93,94] However, recently proposed guidelines agree that biopsy is recommended for suspected Spitz nevi (particularly amelanotic papulonodular lesions) that arise in postpubertal patients and for those with atypical features such as large size (eg, >8-10 mm), excessive growth, asymmetry, or ulceration in patients of any age.[85,93,94]

Optimal histologic evaluation of a Spitz nevus requires a complete specimen, which enables assessment of reassuring features such as symmetry, circumscribed lateral margins, and maturation with depth.[95,96] In a retrospective study on surgical management of Spitz nevi, shave biopsies were more likely to have positive margins (67%; usually the deep margin) than elliptical excisions (28%) or punch biopsies (21%; usually the lateral margin).[97] That said, the majority of the 2010 survey respondents and other experts do not recommend re-excision after incomplete removal if the biopsy sample allowed the diagnosis of a typical Spitz nevus to be established with certainty in a child, especially if there is no clinical evidence of residual lesion.[82,95]

Making sense of the Spitz nevus spectrum

Atypical spitzoid neoplasms (ASNs) represent a frustrating type of melanocytic lesion with borderline histologic features indistinguishable from those of melanoma and an uncertain malignant potential.[98] A positive sentinel lymph node biopsy (SLNB) result has not been found to have prognostic significance for ASNs in any age group or for melanomas in children.[99] A recent systematic review found that 39% (119/303) of reported SLNBs in patients (adult and pediatric) with ASNs were positive, but only one of these patients had died after a mean follow-up period of almost 5 years.[100] Of note, small aggregates of melanocytes within regional lymph nodes do not necessarily represent metastatic melanoma, because such deposits (intracapsular/intratrabecular > parenchymal) have been observed in association with nevi ("nodal nevi").[99,101] There is also no evidence to date that further lymph node dissections or adjuvant systemic therapies are of therapeutic benefit for patients with a positive SLNB in the setting of an ASN,[99] and these interventions can result in long-term complications such as lymphedema.[102] In a recent case series from Boston, 24 pediatric patients with ASNs treated with complete excision but no SLNB or lymph node dissections had no recurrences and were all disease free after a mean follow-up period of 6 years.[103]

Several studies of pediatric melanomas have documented a 30% to 40% likelihood of SLNB positivity, remarkably similar to the rate in ASNs.[99] Although prepubertal children diagnosed with melanoma tend to have thicker tumors (more often spitzoid in nature) and a higher rate of positive SLNB than adolescents or adults with melanoma, survival in most series is paradoxically longer in prepubertal patients (overall mean 5-year survival ~90% versus ~50% in adolescents).[7,99,104–106] Spitz nevi, ASNs, and spitzoid melanomas are thought to exist on a spectrum that is biologically distinct from that of banal nevi, dysplastic nevi, and conventional (eg, superficial spreading) melanomas. The difficulty in differentiating ASNs from spitzoid melanomas based on histologic features undoubtedly leads to disease heterogeneity within series of either entity, complicating interpretation of studies. Identifying molecular markers of ASNs with aggressive behavior represents an important goal, with promising methods including array-based comparative genomic hybridization and fluorescence *in situ* hybridization (FISH) probes. Recent studies have found that specific genomic alterations (eg, homozygous 9p21 deletions; 6p25 or 11q13 gains) are associated with aggressive clinical behavior of ASNs.[107,108] In contrast, isolated deletions in 6q23 confer a favorable prognosis.

Somatic activating *HRAS* mutations and/or copy number increases are found in a subset of Spitz nevi and ASNs (especially desmoplastic intradermal lesions; see Table 1), and both *HRAS* mutation and copy number increases have been documented in Spitz nevi arising within a nevus spilus.[109,110] Heterozygous germline mutations in the BRCA-associated protein-1/ubiquitin carboxy-terminal hydrolase *(BAP1)* gene lead to an autosomal dominant tumor predisposition syndrome characterized by spitzoid neoplasms that present during the second decade of life as pink, polypoid nodules with predominantly dermal epithelioid melanocytes. Affected individuals have an increased risk of cutaneous and uveal melanoma, basal cell carcinoma,

mesothelioma, and other malignancies.[111,112] In patients with multiple spitzoid neoplasms with the aforementioned clinicopathologic features, testing for a germline *BAP1* mutation should be considered and management recommendations include periodic ophthalmologic as well as skin examinations, surveillance for other associated cancers, and evaluation of at-risk family members. In a recent study, a heterozygous $BRAF^{V600E}$ mutation combined with biallelic *BAP1* loss was also identified in ~25% (8/32) of *sporadic* ASTs.[113] Recently, fusions involving genes encoding kinases (eg, *ALK, ROS1, NTRK1*) that stimulate oncogenic signaling were found in approximately 50% of lesions across the entire spitzoid spectrum, from Spitz nevi to spitzoid melanomas.[114,115] These fusions appear to promote tumorigenesis rather than malignancy, analogous to $BRAF^{V600E}$ mutations in melanocytic neoplasms (see Table 1), and they provide a potential target for therapy with kinase inhibitors.

Congenital melanocytic nevi

Evolving definitions and concepts of CMN

The size-based classification of CMN was standardized and updated in 2012,[116] with refinement of the giant category that accounts for the majority of melanomas observed in large studies (see later). This system divides CMN into four groups based on the largest expected *adult* diameter, in centimeters: (1) small, <1.5; (2) medium (M1: 1.5-10, M2: >10-20); (3) large (L1: >20-30, L2: >30-40); (4) giant (G1: >40-60, G2: >60). Because CMN typically enlarge in proportion to the child's growth, the final diameter can be predicted by estimating a size increase from infancy to adulthood by a factor of 1.7 on the head, 3.3 on the legs, and 2.8 in other anatomic sites. Quantification of the number of "satellite" nevi (S1: <20, S2: 20–50, S3: >50) and morphologic characteristics (color heterogeneity, surface rugosity, nodularity, hairiness) were also recommended.[116]

CMN are classically defined as being present at birth. Multiple recent clinical series have documented CMN in approximately 2% to 3% of neonates with a variety of ethnic backgrounds,[117–121] confirming the results of older studies. Although small and medium CMN are relatively common, large or giant CMN occur in only approximately 1 in 20,000 to 50,000 births.[122]

Several observations challenge the existence of melanocytic nevi evident at birth as a distinct entity. Melanocytic nevi that first become evident during infancy or early childhood (especially at <3 years of age) have clinical, dermatoscopic (globular/cobblestone > reticular), histologic, and molecular features indistinguishable from those of "true" CMN. Such nevi are referred to as *tardive CMN* or *congenital nevus–like nevi* (CNLN). In a recent study of nevi in 2-year-old children, the subset of lesions present at birth had a larger mean size and higher likelihood of irregular borders than those that appeared later; no other clinical or dermatoscopic features differed significantly between these two groups.[123] The term *CNLN* has also been employed for lesions with clinical (eg, larger than typical acquired nevi, hypertrichotic, palpable) and (if biopsied) histologic features of a CMN when the age of onset is not known. CNLN measuring 1.5 cm or larger (medium size for a CMN) are found in 1% to 4% of older children and adults.[124–126] In an Italian study, 17% of 12- to 17-year-old children (592/3406) had a CMN/CNLN measuring 0.6 cm or larger in diameter.[127]

As noted earlier, somatic activating mutations affecting proteins in the mitogen-activated protein kinase (MAPK) signaling cascade play important roles in melanocytic tumorigenesis (see Table 1). The $BRAF^{V600E}$ mutation is found in the majority of small CMN, CNLN, acquired melanocytic nevi, and superficial spreading melanomas.[128] In contrast, 85% to 95% of large and giant CMN have somatic activating mutations in the *NRAS* proto-oncogene, with the same mutation found in associated satellite nevi, central nervous system (CNS) lesions, proliferative nodules, and melanomas.[129–133] Activated NRAS signals through both MAPK and phosphatidylinositol 3-kinase (PI3K)/AKT pathways, whereas activated BRAF stimulates only the MAPK pathway. In addition to increasing cell proliferation, the PI3K/AKT pathway promotes melanocyte survival and directional migration, which may contribute to the large and widespread melanocytic lesions observed in NCM. Of note, blue nevi (including congenital cellular lesions) often have activating mutations in genes encoding G protein α-subunits that lead to increased MAPK signaling (see Table 1).

Revisiting the speckled lentiginous nevus

Speckled lentiginous nevi (SpLN; nevus spilus) have a prevalence of approximately 2% to 3%, and are considered to represent a subtype of CMN.[134] Large SpLN often have patterns of distribution reflecting their origin during embryonic development, such as block-like with a sharp demarcation at the midline. The café-au-lait spotlike background of a conventional SpLN is usually noted at birth or in early childhood, with multiple smaller spots progressively appearing over time. The superimposed pigmented lesions can range from lentigines and banal acquired nevi to Spitz and blue nevi. In other SpLN, the spots are small and medium classic CMN, occasionally with a subtle background field of hyperpigmentation that takes time to become apparent (Figure 4). Forms of SpLN with exclusively macular speckles (a component of phacomatosis pigmentovascularis) or papular as well as macular speckles (a component of phacomatosis pigmentokeratotica) have been described.[135]

Conventional SpLN as well as the SpLN (and sebaceous nevi) of phacomatosis pigmentokeratotica are characterized by a postzygotic activating *HRAS* mutation.[136,137] In contrast, a particular activating *NRAS* mutation (different from those typically seen in classic large/giant CMN) has

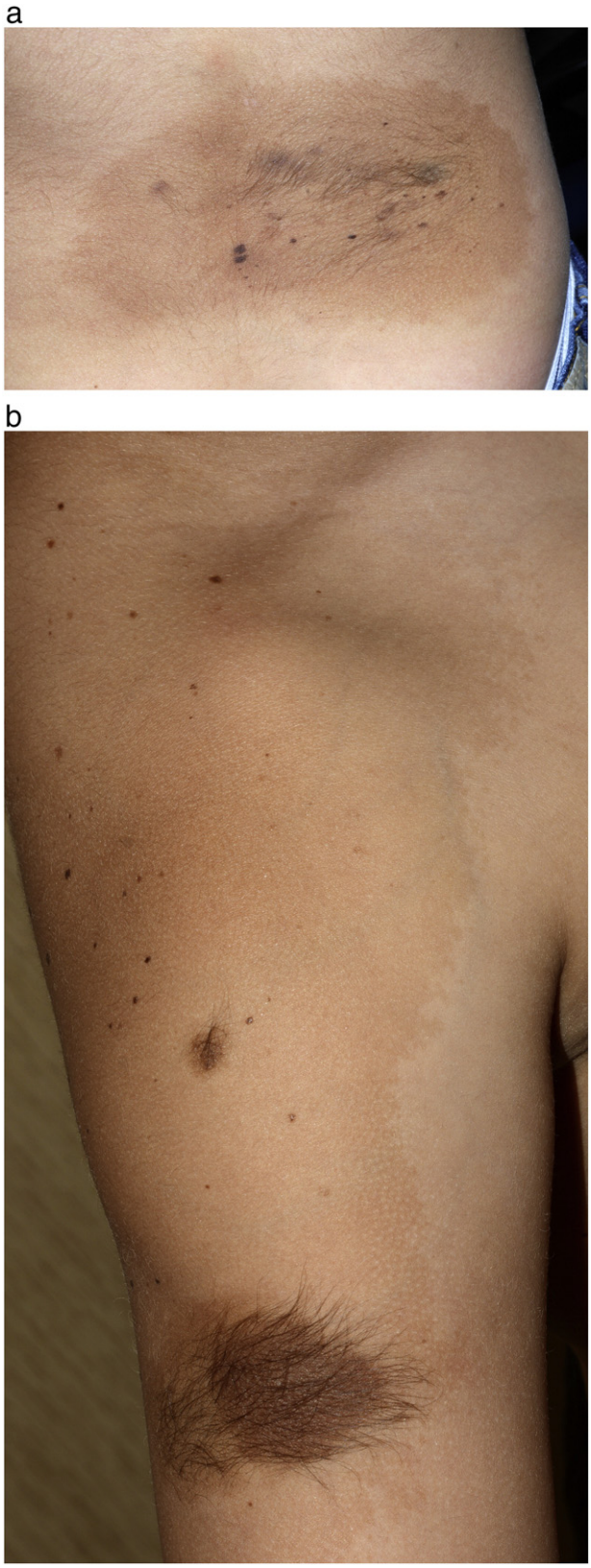


Fig. 4 Speckled lentiginous nevi with features of classic congenital melanocytic nevi (CMN), including hypertrichosis and subtle background patches, which became more evident over time. Note the variable sizes and colors of the superimposed macules, papules, and plaques.

been documented in both the macular background and superimposed nevi of large "CMN-type" SpLN (also referred to as nevus spilus-type CMN).[138] As with classic CMN (see later), the risk of developing melanoma within a SpLN is thought to be proportional to the size of the entire lesion (ie, the background field).[134,136]

The dynamic natural history of CMN

CMN commonly undergo morphologic changes over time. They may begin as flat, evenly pigmented patches or thin plaques and later become more elevated with lighter, darker, or mottled pigmentation and a mammillated, rugose, verrucous, or cerebriform surface. Some authors have noted a particular tendency of CMN in children with fair skin to lighten over the first decade of life.[139,140] CMN can develop superimposed papules and nodules, occasionally with concerning features (eg, rapid growth, ulceration, black or red color) that require biopsy to exclude the possibility of melanoma. Peripheral nerve sheath differentiation (neurotization) of dermal melanocytes commonly leads to the development of soft nodules or large plexiform neurofibroma-like plaques (Figure 5).[141] Lipomatous growths have also been reported in association with a large/giant CMN, underscoring the pluripotent nature of neural crest–derived cells.[142,143] Conversely, a decrease in the thickness of the subcutaneous fat underlying a large or giant CMN is sometimes observed.

The evolution of CMN during the first few months of life can be especially volatile. Transient erosions or ulcerations may develop in medium and larger CMN due to increased skin fragility during the neonatal period (Figure 6).[144] The skin breakdown is usually evident at birth or within the first few days of life, favors the thickest portion of the nevus, and heals within a few days to weeks. Bulky or numerous nodules are sometimes present at birth in patients with a giant CMN located on the back, buttocks, or genitalia.[140,141,145] Benign proliferative nodules can also arise within large CMN during infancy, and the histologic features of these lesions occasionally simulate melanoma or rarely an undifferentiated spindle cell neoplasm.[132,146–148] Comparative genomic hybridization (CGH) showing no chromosomal aberrations or only numeric changes, rather than the structural changes that characterize >95% of melanomas, may help to support the benign nature of such melanocytic proliferations.[147–149] Of note, CGH analysis can be performed on DNA extracted from paraffin-embedded tissue.

CMN located on the scalp have a particular tendency to gradually lighten and regress over time. In two series, complete or almost complete clinical resolution of medium to large CMN on the scalp was observed before age 4 years (mean, 30 months) in seven children.[66,150] Histologic evaluation in two of these patients found that melanocytes remained in the deep dermis and within adnexal structures, with no evidence of inflammation or fibrosis.[150]

The "halo" phenomenon represents a means by which CMN in any site can regress via an immune response to

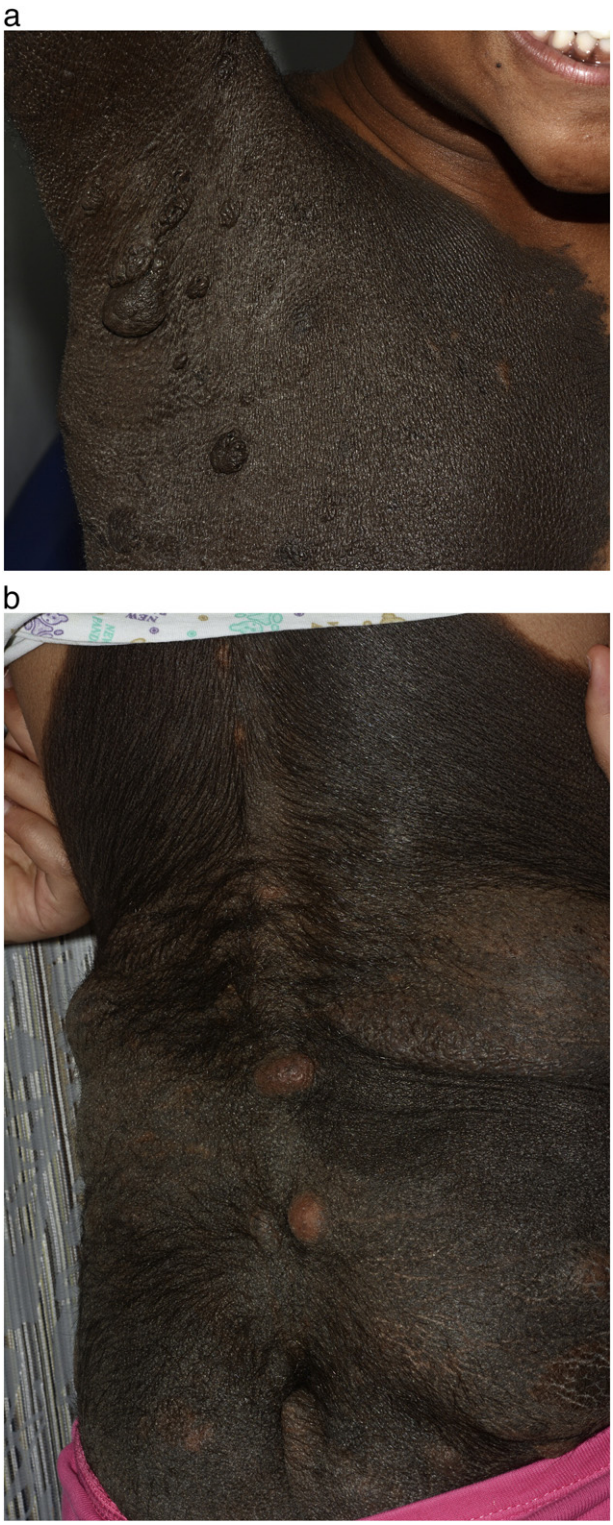


Fig. 5 Giant congenital melanocytic nevi with neurotization. a, Small, soft, exophytic nodules in the axilla. b, Bulky overgrowth resembling a plexiform neurofibroma.

melanocytic antigens. Development of a depigmented halo, which may be symmetric or asymmetric, around the CMN heralds lightening and eventual flattening of the nevus over a period of months to years.[151] In some patients, the halo may

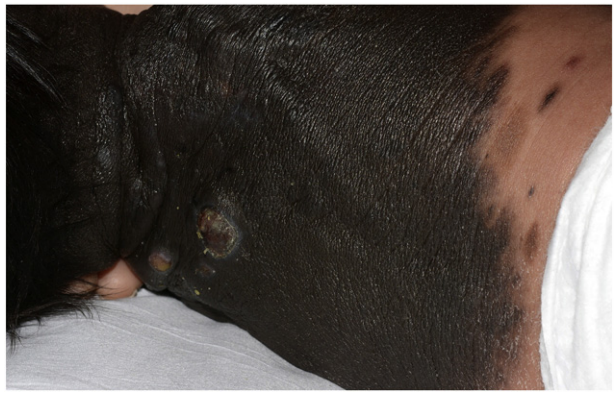


Fig. 6 Erosions and superficial ulcerations on the back of a neonate with a giant congenital melanocytic nevus.

be preceded by an inflammatory phase with scaling and crusting.[152] The desmoplastic hairless hypopigmented variant of CMN also tends to undergo spontaneous resolution.[153,154] These nevi are characterized by woody induration, alopecia, progressive loss of pigmentation, and intense pruritus. In addition, linear scarlike streaks can arise spontaneously within larger CMN, and increased mast cell density has been observed and hypothesized to have a role in pruritus and healing responses in patients with large/giant CMN.[155]

Melanoma risk associated with small and medium CMN

Melanomas associated with small and medium CMN tend to occur after puberty, typically arising at the dermal-epidermal junction with a predilection for the periphery of the nevus.[140,156,157] The risk for the development of melanoma within small and medium CMN is less than 1% over a lifetime.[156,158–161] In comparison, the overall lifetime risk for melanoma in the United State population is more than double this at greater than 2%.[4] In three large cohort studies of patients with a small or medium CMN who were followed for a mean of 13.5 years (n = 680 patients; mean age at entry ~10 years), no melanomas were observed.[158,159,161] Likewise, over a period of more than 30 years at the Massachusetts General Hospital and New York University Pigmented Lesion Clinics, no patient younger than 20 years of age developed a melanoma within a congenital nevus smaller than 5 cm in diameter.[162,163]

Melanoma and other malignancy risk associated with large and giant CMN

In contrast to small and medium CMN, melanomas that arise within large and giant CMN more often develop deep in the dermis or subcutaneous tissue, which can make early detection difficult. Based on multiple large prospective and retrospective cohort studies, the lifetime risk of melanoma

(cutaneous or extracutaneous) associated with a large or giant CMN is thought to be less than 5%.[158,164–172] The selection bias inherent in small retrospective series based in tertiary referral centers likely contributed to prior estimates of higher risk.[156,171–173]

Approximately half of melanomas in patients with a large or giant CMN are diagnosed during the first 5 years of life,[165,166,173] although misinterpretation of proliferative nodules with atypical histologic findings as melanoma may occur in this age group.[139] Melanomas are most likely in patients with CMN that have a projected adult size of more than 40 to 60 cm in diameter, accounting for approximately 75% of CMN-associated melanomas in large series.[158,166,167,171,172] Additional risk factors for melanoma include a truncal location and numerous (eg, >20) satellite nevi.[158,166,167,171,172] Melanomas are less common in patients with CMN that are restricted to the head and neck or an extremity, and melanoma within a satellite nevus is extraordinarily rare.[158,167] The 42 melanomas in patients with large/giant CMN (N = 1756) that were reported in large series during the past 25 years were diagnosed at a median age of 5 years (range, birth to 70 years) and had the following primary sites: 69% (29) CMN on the trunk; 7% (3) CMN on the head/neck; 2% (1) CNM on an extremity; 10% (4) CNS; 5% (2) retroperitoneum; 8% (3) unknown.[158,159,164–167,169,170] Other malignancies that occasionally occur in association with large CMN include rhabdomyosarcomas, liposarcomas, and malignant peripheral nerve sheath tumors.[174–176]

Neurocutaneous melanocytosis associated with large and/or multiple CMN

Neurocutaneous melanocytosis (NCM) represents proliferation of melanocytes in the CNS in addition to the skin in patients with CMN. Melanocytes are physiologically present in the pia mater of the meninges, which is the primary location of brain involvement in NCM. Individuals with both cutaneous and CNS melanomas are excluded from diagnosis of NCM due to the possible metastatic origin of the brain lesions.[177]

The presence of *numerous CMN*, regardless of whether or not there is a large or giant "mother ship" CMN, represents the strongest risk factor for NCM (Figure 7). Approximately two thirds of patients with NCM have a large CMN accompanied by satellite nevi, and the remainder have many small to medium CMN (most often >10 lesions).[177,178] Patients with more than 20 satellite nevi associated with a large/giant CMN have a fivefold higher risk of NCM compared with individuals with 20 or fewer satellites.[179,180] An increased risk of NCM has also been noted in patients with CMN that have a final size of more than 40 cm or (in some studies) a posterior axial location.

NCM is divided into symptomatic and asymptomatic forms, with brain involvement detected via MRI screening in the latter group. MRI findings of NCM can include foci on increased T1 signal within brain parenchyma (especially the temporal lobes/amygdala), obvious masses, and gadolinium enhancement of diffusely thickened meninges (associated with a worse prognosis).[181,182] CNS abnormalities such as Dandy-Walker malformation and posterior fossa cysts are occasionally evident. Recent studies have drawn attention to spinal abnormalities such as tethered cord, intraspinal lipoma, and arachnoid cysts in patients with large/giant CMN.[182–184]

Approximately 4% of patients with high-risk CMN develop *symptomatic NCM*, which has a poor prognosis even in the absence of melanoma. These patients usually present with seizures, hydrocephalus, and signs of increased intracranial pressure (eg, vomiting, headache). Symptoms develop at a median age of 2 years, although individuals with a discrete intracranial mass tend to become symptomatic later (median age, ~10 years) and are more likely to have focal

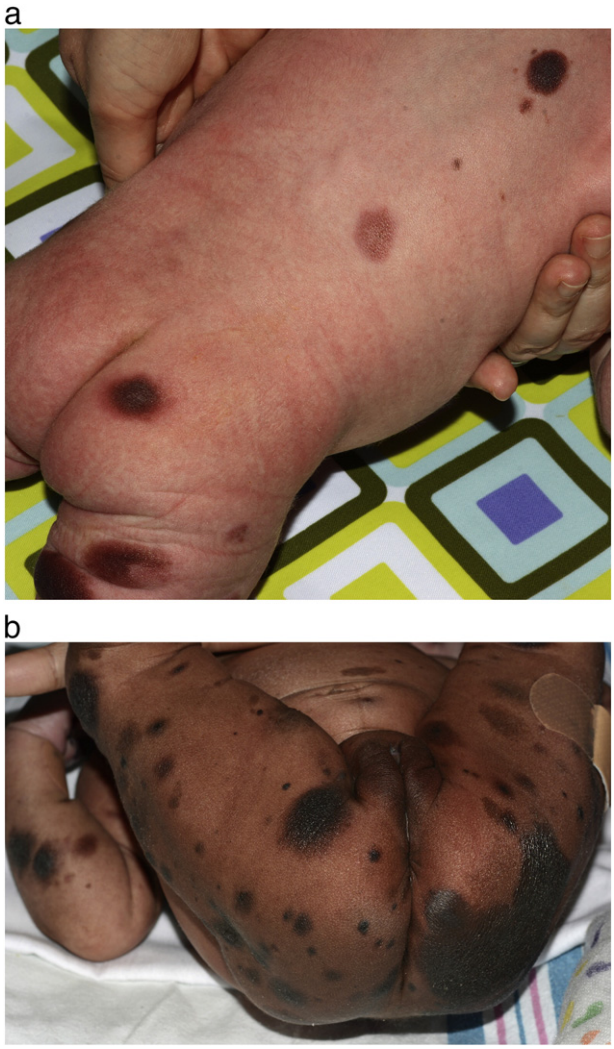


Fig. 7 Patients at risk of neurocutaneous melanocytosis. a, Multiple medium-sized congenital nevi (>20) scattered on the body without a "mother ship" nevus. b, Numerous satellite nevi associated with a large congenital nevus on the back.

sensorimotor deficits.[185] Neurologic findings such as developmental delay, seizures, and abnormal muscle tone are observed in approximately 15% of children with high-risk CMN, including a subset of those with normal brain magnetic resonance imaging (MRI) examinations.[182,186]

Asymptomatic NCM can be diagnosed based on MRI evidence of CNS melanosis in 5% to 25% of infants and children with high-risk CMN.[181,186-189] Due to the paucity of longitudinal studies, the prognostic implications of a negative or positive MRI results in an asymptomatic child are not clear. In one series, 10 patients with asymptomatic NCM diagnosed at a mean age of 6 months were followed for 5 years, and only one individual developed neurologic symptoms.[189]

Screening MRI of the brain and (especially for nevi overlying the posterior axis) spine can be considered in asymptomatic children at high risk for NCM. Sensitivity may be maximized if imaging is performed during the first 6 to 8 months of life, before myelination that may obscure evidence of melanosis, and gadolinium enhancement can help to visualize thickened meninges.[181,186] In addition, at-risk patients should be followed with serial neurologic examinations, head circumference measurement, and developmental assessments.[156,173] MRI is indicated if neurologic symptoms develop and can be repeated as needed to follow progression of findings in asymptomatic patients. Patients with clinical or MRI evidence of NCM may benefit from referral to a pediatric neurologist and, in some instances, a neurosurgeon. In one study, more than one third of CMN patients with abnormal MRI findings required surgical intervention.[186] Treatment strategies targeting MAPK (eg, MEK inhibitors) and PI3K/mTOR (eg, sirolimus) pathways could have potential benefit in patients with symptomatic NCM.[190,191]

Considerations in the management of patients with small and medium CMN

Patients with small and medium CMN can be managed on an individual basis depending on the factors listed in Table 2.[140,173] The author and others do not recommend routine prophylactic excision of small and medium CMN.[156,163,192,193] Baseline photographs and dermatoscopy can be helpful in surveillance of these nevi by physicians. Periodic evaluation is most important after puberty because the risk of melanoma arising during childhood is extremely small. Patients and parents should be instructed in (self-) skin examination and advised to bring focal changes in the color, border, or topography (eg, a red or black papule) of their CMN to the attention of a physician.

When desired (eg, for cosmetic reasons), small and smaller medium-sized CMN can usually be removed via simple excision with primary closure. Serial excision or flap reconstruction may be required for the removal of larger medium-sized CMN and can improve the cosmetic and functional outcome for lesions in technically challenging locations.[192] It is important to counsel patients and parents so that they have realistic expectations regarding the resulting scar and, if removal is prompted by cosmetic concerns, to discuss the degree to which the appearance would likely be improved (eg, scar versus thin tan nevus *or* scar versus thick, verrucous, dark brown nevus). Laser therapy (see later) may represent an option for cosmetically problematic CMN when excision is not an option, especially for relatively thin facial lesions.

Considerations in the management of patients with large and giant CMN

For patients with larger CMN, early and complete surgical removal is often desired as prophylaxis against the development of melanoma[194]; however, it is usually impossible to remove every nevus cell in these lesions due to their extensive size and the involvement of deeper structures such as fat, fascia, and even muscle. Recurrence of pigmentation in and around the scar is common, and development of melanoma under skin grafts placed after complete excision of a large CMN has been reported.[167,195] Because primary melanomas can arise in the CNS and other extracutaneous sites in patients with large/giant CMN, even theoretically complete excision of the nevus does not eliminate the risk of malignancy. Although a trend toward lower incidence of melanoma in patients whose nevi were partially or completely excised has been noted in several studies,[194] the largest nevi, which have a higher risk of developing melanoma, are also more likely to be inoperable.[158,196]

Recently, there has been increased recognition of the need to carefully consider both potential benefits and treatment-related morbidities for each individual patient when making decisions regarding surgical intervention for large/giant CMN.[140,156,193,197–200] Patients and parents may feel that scars are cosmetically and socially more acceptable than the nevus, especially for facial lesions.[139,193,200] Excision of nevi or portions of nevi that are bulky or pruritic may also have functional benefit.

However, surgical procedures can result not only in short-term discomfort, limitation of physical activity, and risk of infection, but also in long-term complications, such as scars that may restrict joint mobility and impair function.[139,140,193,197–200] The possible benefits of initiating surgical interventions during the first year of life, when there is increased skin elasticity and tissue mobility, must also be balanced with risks associated with general anesthesia.[193,197]

Staged excision (down to fascia) with flap reconstruction after tissue expansion of uninvolved adjacent (or even distant) skin represents the primary surgical approach for removal of large CMN.[140,201] This results in aesthetic and functional outcomes superior to excision with skin grafting or artificial skin substitutes.

Table 2 Factors to consider in the management of small and medium congenital melanocytic nevi

	In favor of excision or *earlier excision*	In favor of *waiting* to potentially excise	In favor of *observation*
Psychosocial/ cosmetic concerns	• Location on the face or other highly visible area [a] – Larger lesion – Conspicuous site (eg, tip of nose) – 'Ugly' lesion (eg, warty, thick)	• Subjectively unappealing lesion in a visible site: let the *patient* decide if bothered by the lesion	• Lesions that are clearly more cosmetically appealing than the surgical scar
Natural history	• Clinically or histologically worrisome changes • Functional issues (eg, bulky, exophytic lesion)	• Site where involution is common (eg, scalp) • Melanoma before puberty is extraordinarily rare	• Evidence of involution • Low lifetime risk of melanoma (<1%)
Ease of monitoring	• Hidden site (eg, buttock) • Black or mottled pigmentation • Thick, irregular, or multinodular surface • Dense hypertrichosis		• Exposed site (eg, forearm) • Light, homogenous pigmentation • Thin, uniform surface
Patient/family's attitude about monitoring	• Reluctant • Inattentive		• Willing • Attentive
Anxiety level	• High level of anxiety about the *lesion*	• High level of anxiety about the *procedure*	
Factors that affect healing/scarring	• In infant, removal desired of lesion in site where tissue extensibility is greatest during first year (eg, distal limbs)	• Sports season currently or in near future	• Risk of functional impairment from scar (eg, over joint, circumferential on limb, eyelid margin)
Anesthesia requirements	• Removal desired and general anesthesia required even if done in adolescent/adult	• Removal desired and local anesthesia possible—variable, but often at age 9–11 years	

[a] Helpful to excise by early childhood (eg, 4–5 years), when body image begins to solidify.

When excision of large/giant CMN is not feasible, techniques such as curettage, dermabrasion, and ablative (eg, carbon dioxide, erbium:YAG) or pigment-specific laser therapy may have cosmetic benefit.[140,202,203] Ablative procedures, which remove the epidermis and upper portion of the dermis, have the most favorable risk/benefit ratio during the first 1 to 2 months of life, when active nevomelanocytes are concentrated within the upper dermis and there is a lower likelihood of excessive scarring.[140,203] It is important to remember that nevomelanocytes remain in the dermis after all these procedures, as evidenced by frequent repigmentation as well as multiple reports of the subsequent development of melanoma in treated areas.[204]

Regardless of whether or not a large/giant CMN is resected (partially or "completely") or treated with other modalities, patients should be followed closely with periodic total body skin examinations. Monitoring can be aided by dermatoscopy and baseline photographs of the large/giant nevus, satellite nevi, and scars. Palpation of nevi and scars to detect firm nodules or focal induration, which may signify the development of a melanoma below the dermal-epidermal junction, is essential. These and other areas with suspicious changes (eg, papules/nodules with rapid growth, red or black color, or ulceration outside of the neonatal period) should be examined histologically.

CMN often have psychosocial ramifications, especially in patients with larger nevi and those located in visible sites such as the face. Children with large or giant CMN are more likely to suffer from anxiety, depression, and social problems.[205] Patients and families facing psychological and medical issues related to CMN may benefit from counseling and internet support groups such as Nevus Network (www.nevusnetwork.org) and Nevus Outreach, Inc. (www.nevus.org).

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