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EXPERT REVIEWS

Analysis of clinical and dermoscopic features in melanocytic lesions with special emphasis on problematic lesions in children

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Most melanocytic lesions in children are considered 'nonproblematic' and are managed conservatively because of their invariable benignity. Congenital melanocytic nevi (CMN) and Spitz nevi are the most problematic pigmented lesions in childhood. Regarding CMN, the biggest risk of melanoma development occurs with increased nevus size, being particularly high in giant CMN, in children younger than 10 years. On the other hand, awareness should be related to new, rapidly growing lesions (the clinical hallmark of Spitz/Reed nevi and melanoma). The aim of this review is to present clinical and dermoscopic features of a large spectrum of pediatric melanocytic lesions with special attention to problematic lesions that may occur in childhood.

KEYWORDS: adolescents • childhood • congenital nevi • dermoscopy • melanoma • Spitz nevi

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Childhood melanoma is a rare occurrence [1,2] and its annual incidence is estimated in 0.8 cases per million in the first decade of life [3]. Nevertheless, accuracy in melanoma detection in children and adolescents still remains low. A recent study has tested accuracy in melanoma detection in childhood using the 'number needed to excise' value, obtained by dividing the total number of excised lesions by the number of melanomas [4]. The overall 'number needed to excise' value in pediatric patients over the 10-year study period was 593.8, meaning that approximately 594 lesions were excised to find one melanoma. This value is 20-times higher than the rates usually found in adult patients, thus suggesting that clinicians should raise their threshold for malignancy when faced with melanocytic lesions in pediatric patients. An effective strategy to reduce unnecessary excision without missing melanoma would be to focus on problematic lesions. Congenital nevi and Spitz/Reed nevi are the most problematic lesions in differential diagnosis with melanoma in childhood [1,4–7]. In particular, large congenital melanocytic nevi (CMN) represent the most important risk factor for melanoma among children younger than 12 years of age with a third of melanomas arising on giant nevi [8–11]. On the other hand, Spitzoid lesions tend to share clinical, dermoscopic and even histopathologic features with melanoma, thus rendering differential diagnosis particularly challenging even for expert clinicians. In this scenario, awareness should be related to new rapidly growing lesions (the clinical hallmark of Spitz/Reed nevi and melanoma) and to congenital nevi with a recent history of changing size, color and/or shape.

Dermoscopy is currently a pivotal tool in the diagnosis of skin tumors, allowing a better sensitivity and specificity in the diagnosis of skin tumors, as compared with naked eye examination. The role of dermoscopy in a pediatric setting is to help differentiate melanocytic nevi and nonmelanocytic skin lesions from melanoma, thus allowing a better accuracy in childhood melanoma detection [12–16]. The aim of this review is to present clinical and dermoscopic features of a large spectrum of pediatric melanocytic lesions with special attention to problematic lesions that may occur in childhood.

Nonproblematic melanocytic nevi

Common nevi

The total number of melanocytic nevi varies with age, following a dynamic course of evolution. Nevus counts and nevus density increase from youth to midlife and thereafter decrease [17,18]. Moreover, upcoming evidence suggests that the morphological

subtypes of nevi are also age-dependent. Traditionally, nevi present at birth or appearing in the first year of life are defined as congenital, whereas those appearing later after birth are defined as acquired. Common acquired nevi are small, flat to slightly elevated, brown lesions that can appear anywhere on the surface of the body. Histopathological examination usually shows that they are either compound or dermal nevi [19].

Several studies have examined the prevalence of dermoscopic patterns in childhood nevi. By dermoscopy, the globular pattern seems to be the most characteristic in childhood, both small congenital and early acquired nevi display a dermoscopic globular appearance [20–22]. Conversely, a reticular pattern usually typifies nevi developing after puberty [20–22]. Zalaudek *et al*. found a prevalence of globular pattern (60%) followed by complex (21%), reticular (12%) and homogeneous (5%) pattern [20]. Scope *et al*. found a homogeneous pattern in 44% of children, followed by globular (37%), reticular (13%) and complex (5%) pattern [23]. Overall, the frequency of globular and reticular patterns increases with age and 'homogeneous' nevi may evolve into patterned nevi [23]. Recently, Scope *et al*. introduced the concept of nevus volatility in childhood, finding that children with higher back nevus counts have greater nevus volatility, being more likely to both develop new nevi and have nevi that disappear during follow-up [24]. Moreover, globular nevi, both congenital and acquired, seem to be more frequent on the upper back than lower back and limbs, thus also suggesting a site-dependent variability of the different dermoscopic patterns [23].

Dermoscopic examination of common nevi in children usually shows no atypical features, and these lesions are managed conservatively. However, it is not rare to find nevi with an eccentric hyperpigmentation, the so-called 'Bolognia's sign' [25]. This feature is frequently found in melanomas, but nevi with eccentric hyperpigmentation show a brown to gray–black homogeneous pigmentation with no other dermoscopic features of melanoma. In addition, this 'innocent' hyperpigmentation may often disappear during follow-up.

Nevi with more pronounced atypical features generally arise after puberty and are present until 40–50 years of age [26–28]. Clinical features of these nevi include: flat or moderately elevated surfaces, heterogeneous color and diameter more than 6 mm. The presence of multiple nevi with atypical features is a marker of increased risk for melanoma development. Therefore, a regular follow-up is recommended after puberty, especially in children presenting additional risk factors, such as high nevus count, positive family history of melanoma, fair skin type and history of sunburns. In this category, the appearance of melanoma is *de novo* and atypical nevi represent the only marker for risk of developing melanoma. The major difficulty consists in identification of incipient melanoma and differentiation from atypical nevi. Tsao *et al*. demonstrated that the possibility of transformation of a nevus into melanoma is quite low; it ranges from a minimum of one in 200,000 in women and men under 40 years of age to a maximum of one in 33,000 in women and men over 60 years of age [29]. Bauer and Garbe estimated lower percentages of transformation in people younger than 20 years of age [16,30,31].

Blue nevi

Blue nevi (BN) are a subset of melanocytic proliferations characterized by dermal dendritic melanocytic cells. Children and adolescents are more likely to develop BN, which have an incidence estimated at 1–2% in the white population. BN occur as two main different groups: common BN and cellular BN [32]. BN usually appear as bluish, smooth surfaced papules, nodules and plaques. The main clinical difference between common and cellular BN is the diameter, with the latter being larger (up to 30 mm) than the former (<10 mm). Cellular BN may also have a polychromatic appearance (i.e., mixed blue, brown and white in color).

Dermoscopic examination of BN shows a typical steel-blue homogeneous coloration generated by the presence of heavily pigmented melanocytes in the dermis; different color variants are also possible [33] always in the absence of any other dermoscopic structure. A mixed blue and white color is frequently seen in dermoscopy in BN of the extremities [34]. Small and common BN do not need further management, while cellular BN, especially when they grow rapidly, can create problems in being differentiated from melanoma, and more so if they present with atypical dermoscopic features. Moreover, BN with a peripheral satellitosis mimicking malignant melanoma (MM) [35–38] have been described. In these cases, excision is necessary to confirm the benign nature of the melanocytic proliferation.

Combined nevi

A combination of two different nevus cell populations at histopathological examination is the hallmark of combined nevi [39]. The most frequent combination is between small congenital and a BN, but also other combinations are possible [40]. Depending on the type of combination, dermoscopy can show different patterns: globules combined with blue homogeneous pattern or reticular pattern at the periphery surrounding a blue colored central area. Due to the doubtful clinical and dermoscopic presentation, these lesions are often excised in order to rule out melanoma.

Halo nevi

Halo nevi (HN; also called Sutton nevi) are congenital or acquired nevi surrounded by a rim of vitiligo characterized, over a variable period of time, by a progressive disappearance of central part of the nevus due to spontaneous regression in which T lymphocytes are considered to play a key role [41–46]. HN show an increased frequency in children and young adults and their preferential location is the trunk, on which they can be multiple. HN are often associated with autoimmune diseases such as vitiligo and Hashimoto thyroiditis, but also with atopic dermatitis and Turner syndrome [47,48].

Dermoscopic examination often shows, in the first phase before the disappearance of the nevus, a globular pattern surrounded by a variably sized rim of scar-like depigmentation. Later on, the central nevus completely involutes and a gray pigmentation due to melanophages and dermal vessels can be seen [49].

Differential diagnosis should be made with halo melanoma and pseudo-halo nevus. Regressive melanoma can sometimes mimic a

halo nevus. Clues to differentiate halo melanomas are the presence of an asymmetric rim of a white scar-like area, that is eccentric and is not well defined as in HN. In addition, the remnants of the melanocytic lesion show atypical dermoscopic features, suggesting the diagnosis of regressive melanoma.

Pseudo HN are artifactual HN produced by sunscreen application exclusively on a common melanocytic nevus (Figure 1) [50].

Nevi on special locations

Melanocytic skin lesions can develop anywhere on the surface of the body. The dermoscopic patterns of nevi essentially reflect the histopathologic distribution of the pigmented structures within the skin layers. As a consequence, when appearing on special body areas, namely, body areas with peculiar anatomical structures (face and acral sites), nevi display distinct dermoscopic patterns different from those usually found on the trunk. Scalp and mucosal areas are also considered special body areas, because melanocytic lesions developing on these areas frequently show concerning features by histopathology that may overlap with melanoma.

The most common patterns of nevi developing on acral sites (palms and soles), on the scalp and on mucosal areas, will be described in the following sections. Facial melanocytic lesions are usually considered in differential diagnosis with melanoma of the lentigo maligna type, a particular type of melanoma that usually develops in adults and elderly patients, thus facial lesion are not discussed in this review.

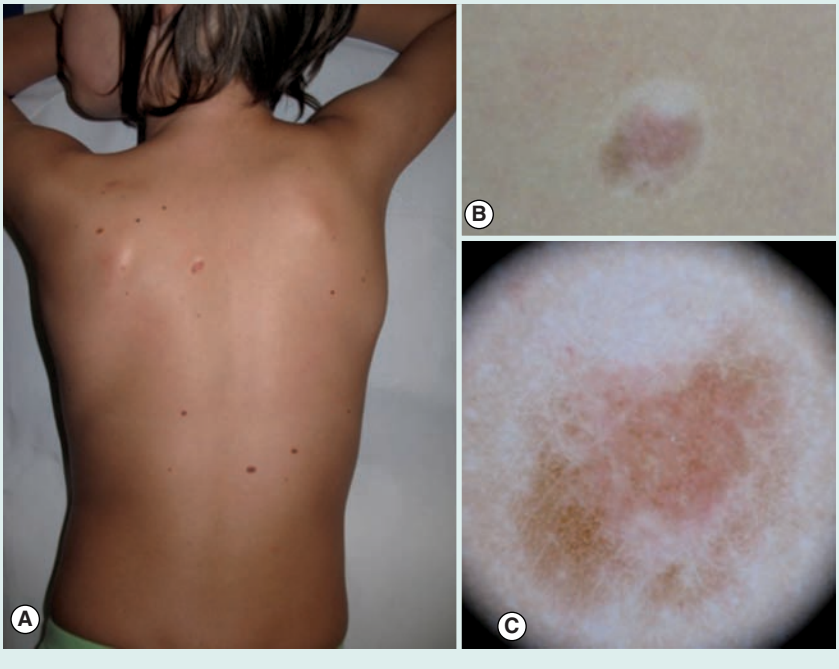

Figure 1. Clinical and dermoscopic image of a halo nevus on the back of a 4-year-old girl. (A) Clinical overview. **(B)** Close-up clinical image showing a pigmented lesion surrounded by a whitish halo. **(C)** With dermoscopy, the lesion appears almost completely involuted, with a homogeneous pattern, surrounded by a rim of scar-like depigmentation.

Acral nevi

Melanocytic lesions developing on palms and soles usually display a parallel pattern due to particular anatomical structures inherent to this location [51,52]. The pigmentation may follow the furrows as well as the ridges of glabrous skin. In particular, the parallel furrow pattern, the lattice-like pattern and the fibrillar pattern are commonly found in acral melanocytic nevi, whereas the parallel ridge pattern is highly suggestive of melanomas on acral sites [53]. Acral nevi can usually be managed conservatively. Of note, acral congenital nevi may present a palpable area in the center of the lesion, sometimes displaying a grayish coloration that can represent a matter of concern for clinicians, and corresponds to a dermal component of the nevus. In these cases, differential diagnosis between a parallel ridge and a parallel furrow pattern can be made easier by evaluating the distribution of the pigment at the periphery of the lesion (Figure 2).

Scalp nevi

Scalp nevi in children and teenagers are known indicators for a higher total nevus count, being considered as a marker of the so-called 'moley child' [54,55]. Thus, teenagers with scalp nevi may benefit from regular whole-body skin examinations. Moreover, a subset of scalp nevi may reveal worrisome features on histopathology, although they have no documented risk for malignant transformation [56]. Common scalp nevi in children and teenagers typically reveal a pigmented network with perifollicular hypopigmentation that may give rise to some border irregularity of the nevus or a uniform globular pattern. Children and adolescents with fair skin types may present scalp nevi with central hypopigmentation, also called eclipse nevi. Dermoscopically, eclipse nevi show a central area of hypopigmentation, sometimes with a keratotic surface, which is surrounded by a brown pigmented network of different color intensity. These lesions can usually be managed conservatively (Figure 3).

Mucosal lesions

Melanocytic skin tumors of the mucosa, in particular the vulva and penis, reveal peculiar clinical and epidemiological characteristics different from those of other body sites. Only a few studies have examined specifically the dermoscopic features of melanocytic lesions in these body areas [57–59].

All studies agree in indicating age as a strong predictor of the benignity or malignancy of the lesions. Nevi seem to be strongly associated with younger age compared with melanoma or melanosis. By dermoscopy, the combination of blue, gray or white color with structureless zones are the strongest indicators of malignant mucosal

lesions. Nevi usually exhibit a globular/cobblestone pattern or mixed pattern. Of note, a small subset of benign vulvar nevi, known as atypical melanocytic nevi of the genital type, show concerning features by histopathology that may overlap with melanoma. These lesions may present a mixed pattern by dermoscopy, with a homogeneous brown–gray pigmentation or globules. Thus diagnosis and management should be based on a good clinical, dermoscopic and histopathologic correlation, taking into account the age of the patient, in order to avoid over-diagnosis of melanoma in this special body area (Figure 4).

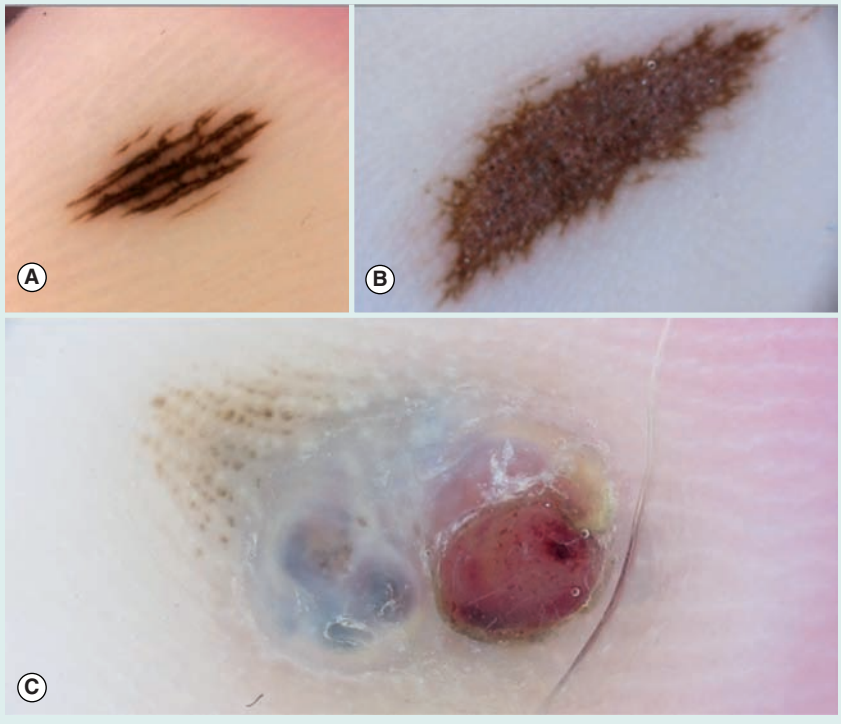

Figure 2. Dermoscopy images of three acral lesions. (A) A small acquired acral nevus showing a parallel furrow pattern. **(B)** Congenital acral nevus presenting a palpable area in the center of the lesion and displaying a grayish coloration by dermoscopy, corresponding to a dermal component of the nevus. At the periphery, a parallel furrow pattern can be detected. **(C)** Dermoscopy of an acral melanoma, arising on a pre-existing nevus. The melanoma was growing as a nodular component displaying a blue–white veil and an ulcerated red area.

Problematic melanocytic nevi

Congenital nevi

CMN are considered, by some authors, to be neural crest-derived hamartomas, which are visible at, or shortly after birth as pigmented tumors [60]. The incidence of any size of CMN of neonates ranges from 0.2 to 2.1% incidence of CMN in neonates regardless of nevus size [58]. They are categorized according to the maximum diameter of the nevus; small (<1.5 cm), medium (1.5–20 cm) and large (>20 cm) CMN [60]. The latter group may be further classified as G1 (20–30 cm), G2 (30–40 cm) and G3 (>40 cm).

The risk of malignant transformation is a matter of ongoing debate. Evidence suggests that the risk increases with the size of the nevus; moreover, the age of onset and depth of origin of MM seem to differ in relation with the size of the nevus. In summary, the risk of MM development is higher for giant CMN than for small- and medium-size nevi; MM arising in CMN tends to develop at younger age and to originate deep within large CMN and superficially within small or medium sized CMN. However, more data are necessary before drawing conclusions. The authors report the most recent evidence about incidence and risk of MM development within large- and small- to medium-sized CMN in the following sections (Figure 5).

Giant CMN

Many studies have been conducted on the risk of melanoma associated with giant CMN [60–62]. The magnitude of the risk for large CMN varies widely between studies (0–50%) [60]. Two important meta-analyses have been conducted in recent years [61,62]. A 2003 review of eight studies (432 giant CMN patients) found that 12 patients (2.8%) developed melanoma during the reported follow-up periods [61]. Of the 12 patients who developed melanoma, ten developed it within their giant CMN, while data were unavailable/unknown for the other two patients. In 2006, Krengel *et al.* analyzed 14 studies with a total of 6571 CMN patients who were followed for a mean of 3.4–23.7 years and found that 46 (0.7%) developed

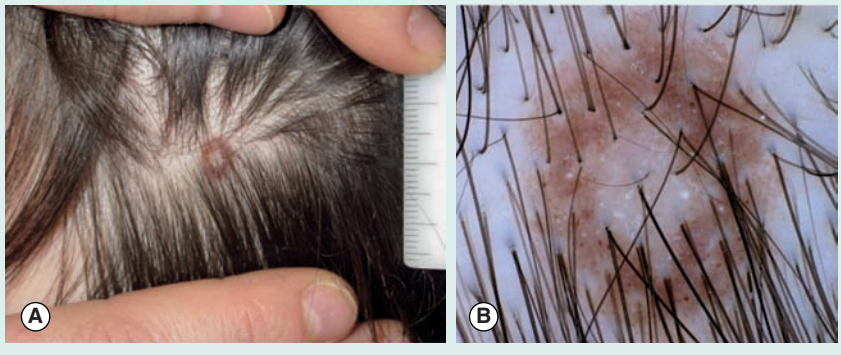

Figure 3. Eclipse nevus on the scalp of a 12-year-old boy. (A) Clinical view with presence of a white central area surrounded by a rim of brown pigmentation. **(B)** Under a dermoscope, the lesion shows a pigment network with perifollicular hypopigmentation, and scattered homogeneous brown globules. At the center, a hypopigmented, white area is detected.

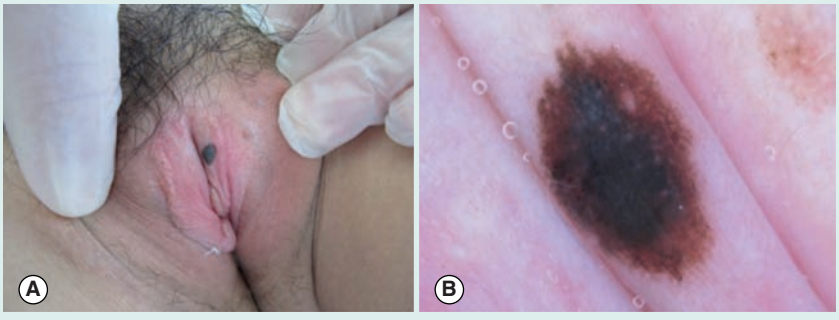

Figure 4. Compound melanocytic nevus of the genital area in a 13-year-old girl. (A) Clinical image showing a dark brown macule on the labia. **(B)** On dermoscopy, the lesion shows a mixed pattern with a homogeneous brown pigmentation and a central blue–grey area.

a total of 49 melanomas (mean age at diagnosis: 15.5 years; median age: 7 years). The authors found a markedly increased relative risk (465) of developing melanoma during childhood and adolescence [62].

Concerning the depth of origin of CMN-associated MM, many believe that MM developing within giant CMN arise from a greater depth [63]. However, data on this hypothesis appear limited at this time. Prospective data are completely lacking, and there are no large series that compare origins of melanomas among nevi of different sizes.

Large CMN are known to sometimes be associated with systemic diseases, and in particular with neurocutaneous melanocytosis (NCM). NCM is a melanocytic proliferation involving the CNS, usually associated with multiple CMN [64]. The presence of NCM could alter the prognosis of the affected patients due to an increase of intracranial pressure. A fatal outcome has been reported in more than half the patients affected by symptomatic NCM; death occurred within about 3 years after the appearance of symptoms, mostly in individuals younger than 10 years of age [16,65].

Brain MRI is indicated for patients at risk for NCM. Although a positive result will be given in about 23% of patients with no neurologic symptoms; only a minor rate of patients will subsequently develop a symptomatic NCM [16,66]. Conversely, a negative MRI does not permit to rule out the possibility of symptoms developing later. It has been suggested by some authors that periodical MRIs would be useful in patients at risk, although clinical examination could also be sufficient. MRI may be also useful in patients affected by symptomatic NCM that could be eligible for surgical treatment due to ameliorate symptoms. Moreover, in children with large- or medium-sized nevi affecting the lumbosacral region, MRI could be used to detect spinal abnormalities such as tethered cord syndrome [16,67].

Originating from large CMN, nodules may appear in the context of nevus often clinically and dermoscopically mimicking melanomas. A wide variety in size, rapid growth, potential ulceration and difficulty to histologically distinguish them from melanoma are characteristic of these nodules [16].

Nodular proliferations can show four different patterns of presentation [16,68]: lesions mimicking superficial spreading melanomas, histologically characterized by the presence of large epithelioid melanocytes in the upper dermis and sometimes spreading to epidermis in a pagetoid way; lesions mimicking nodular melanomas, characterized by a nodular proliferation of large melanocytes with uniform nuclei in the dermis; proliferative neurocristic hamartomas with deep proliferation in dermis and subcutaneous tissue, characterized by a changeable degree of neural or mesenchymal differentiation; true melanomas, mostly showing small blast-like melanocytes, whose features are scan cytoplasm, hyperchromatic nuclei and high mitotic rate [16].

Chromosomal abnormalities of atypical nodules compared with CMN and true melanomas arising on CMN were studied by Bastian *et al.* [16,69]. The genomic differences among these three groups could become useful in histologically doubtful cases. Chromosomal aberrations were commonly found in atypical nodules, rather than classic CMN in which they were absent [16]. Moreover, the authors noticed that there was a qualitative difference in chromosomal aberrations, with structural changes predominating in melanomas, and abnormalities in the number of chromosomes being mostly frequent in proliferative nodules [16,69].

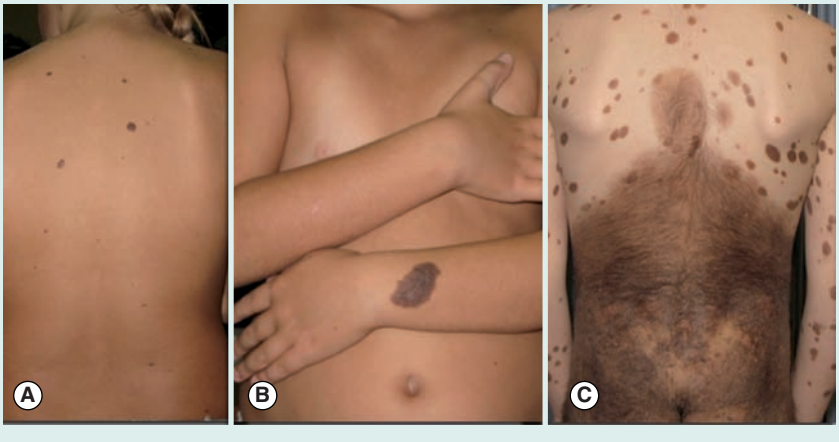

Figure 5. Congenital melanocytic nevi. (A) Small (<1.5 cm diameter) congenital nevi on the back of an 8-year-old girl. **(B)** Medium size (1.5–20 cm) congenital nevus on the arm of an 8-year-old girl. **(C)** Giant congenital nevus (>20 cm), involving the area of the buttocks and the back, in a 9-year-old boy. Of note, the presence of multiple satellite nevi can be noticed.

Small & medium CMN

There is a lack of consensus on the risk of developing melanoma in these groups of nevi; it has been estimated that up to 1% of patients with small and medium CMN will develop a melanoma over a lifetime [69–77]. Other physicians consider the risk of melanoma development related with age; children younger than 10 years have an incidence of approximately 0.7 per million, while for children aged 15–19 years, the incidence increases up to 13.2 per million [16,70]. When there are no abnormalities at clinical and dermoscopic examination, these lesions can be managed conservatively, if the patient is compliant to follow-up and no cosmetic alteration is present [16]. Lesions should be followed up with clinical examination annually, and eventually with digital dermoscopy. Moreover, parents should be informed on the increasing size of the nevus proportional to the body growth of the affected child [16].

Diagnosis & management

At clinical examination, diagnosis of medium and large CMN is simple, considering their size and appearance since birth [16,78]. Dermoscopy will in most cases, show a globular or cobblestone pattern. Different patterns, such as reticular pattern, mixed reticular/globular pattern and diffuse pigmentation, can be present in medium CMN. Lesions appearing at lower limbs usually show a reticular pattern. Further dermoscopic features commonly seen in CMN are: small brown dots typically seen within the network meshes, comma-like vessels, milia-like cysts and hypertrichosis [16]. The management of CMN needs individualization, taking into consideration the patient's age, nevus size, location and depth, risk for malignant transformation, risk for NCM, ease of examining the nevus for suspicious changes, cosmetic and psychological impact associated with the presence of the CMN and/or the presence of aesthetically displeasing surgical scars [78].

For large CMN, surgical excision could be performed to prevent melanoma development. When nevus size is too large and complete excision is not possible, a staged excision could be made. Some authors recently challenged the recommendation of surgically removing large CMN due to the scarce prevalence of melanoma developing from CMN [78].

Treatments alternative to surgery include dermoabrasion, curettage, chemical peels and laser therapy [78]. Dermoabrasion consists of removing the whole epidermis and upper dermis to eliminate the superficial melanocytic cells. It is preferentially performed during infancy. However, this technique leaves the skin more fragile, thinner, tender and with lower hair density [16,79]. With curettage, superficial dermis, in which there is a high concentration of melanocytes, is separated from deep dermis through a natural cleavage plan, present only in the first weeks of life [16,80]. After curettage, a dense and sclerotic connective tissue replaces the removed dermis. Chemical peels could produce a reduction of the melanocyte number and is indicated in light pigmentation CMN [16,81]. Renal and cardiac toxicity must be listed among the side-effects of this treatment. Regarding laser therapy, Q-switched ruby laser is the most commonly used laser in treatment of CMN, because of its wavelength, it is selectively adsorbed by melanin [16]. Scarring is an uncommon outcome of this treatment, although repigmentation may appear in most treated patients, producing a final depigmentation rate of about 50% [16,82].

Alternatively, annual clinical and dermoscopic follow-up can be suggested; however, because of the greater depth of origin of MM arising within large CMN, early recognition of MM is virtually impossible in these cases. On the contrary, in small- and medium-sized CMN, assuming that melanoma develops superficially within the nevus, dermoscopy can be useful to detect early changes within the nevus before they appear clinically visible, thus allowing an early diagnosis and prompt surgical excision of suspicious lesions. Common dermoscopic features of early MM arising on congenital nevi are the development of a blue–white veil, regression structures and/or atypical vascular pattern.

Spitz/Reed nevi

The term 'Spitz nevus' derives from Sophie Spitz, who in 1948 first described pediatric melanocytic lesions that histologically resembled melanomas and yet lacked their aggressive behavior. Currently, the clinical histology of Spitz-type lesions has become tremendously complex. We recognize, from both clinical and histopathologic points of view, a spectrum of Spitzoid lesions. On one end we find common Spitz/Reed nevi, melanocytic proliferations that frequently occur in children and are histopathologically classified as benign. On the other end, we recognize 'Spitzoid melanomas,' a morphologic type of melanomas with Spitzoid features, which are readily identified as malignant on histopathologic examination. In between these two extremes, we place a series of Spitzoid lesions that present varying features of clinical and histopathologic atypia and unknown malignant potential. These intermediate forms of Spitzoid lesions have been referred to with a variety of terms such as 'Spitz nevus with atypia', 'atypical Spitz nevus', 'atypical Spitz tumors' (AST) and melanocytic tumors of uncertain malignant potential. Currently, some authors have suggested the term of AST as the more widely accepted; however, no adequate histologic criteria exist to clearly classify these lesions as benign or malignant, and even expert dermatopathologists are unable to reliably predict the outcome of this group of atypical Spitz lesions based on morphologic criteria. These uncertainties are the major reason why evidence-based management guidelines for Spitz tumors have not been established until now. The current state-of-the-art recommendation for management regarding clinical, dermatoscopic and histopathologic features of Spitzoid lesions are summarized in the following sections.

Classic Spitz/Reed nevi

Spitz nevus, in its classic definition, is considered as a pinkish or flesh-colored papular or nodular lesion characterized by a rapid growth, usually located at lower limbs or face, appearing in children or early adulthood [16,83–86]; the main histopathologic feature is the presence of large spindle and/or epithelioid cells associated with poor or absent melanin [16]. The eponym 'Reed nevus' refers to a benign melanocytic lesion originally described in 1975 as 'pigmented spindle cell nevus' [16,87]. It is typical of young adults, presenting as a rapidly growing brown-to-black macular

or papular lesion, often appearing on the lower limbs; at histopathologic examination, it presents characteristic interconnecting junctional fascicles of heavily pigmented spindle cells [16]. Some authors have challenged the independence of Reed nevus from Spitz nevus due to the description of heavily pigmented spindle or epithelioid cells [16,88], therefore also assigning Reed nevus to the larger spectrum of Spitz nevus [16]. To date, authors are still considering Reed nevus as a different nosologic entity, which, in their opinion, is distinguishable from pigmented Spitz nevus [16,85,89–95]; however, it still remains a debated question to distinguish, by histopathological examination, these two clinical entities although no relevant clinical and dermoscopic differences exist [16,89]. On the basis of the aforementioned discussion, Spitz nevus can be divided into two categories: classical and the pigmented type (comprising Reed nevus) [16].

Spitz/Reed nevi can present at dermoscopic examination with six main different patterns: globular, vascular, reticular, starburst, atypical and homogeneous [96,97]. Spitz nevus classically presents as an amelanotic or hypopigmented lesion characterized by the presence of dotted vessels that constitute its vascular pattern [98], responsible for its typical pink color. These vessels are typically monomorphic, homogeneously distributed in the context of the lesion, frequently grouped and encompassed by white lines that regularly intersect, forming the so-called 'reticular depigmentation'. Additional features are a slight pigmented background with a diffuse brown-to-gray hue associated with gray–brown, small- to medium-sized globules, which are extensively and regularly spaced alongside each other.

Reed nevi appear very different dermatoscopically. Their initial pattern is globular or a starburst, the latter characterized by peripheral pigmented lines regularly arranged like an exploding star. During monitoring, the starburst pattern disappears and a homogeneous or reticular pattern is seen with streaks and pseudopods gradually less evident. The observed changes in dermoscopic patterns appear to represent different phases of the natural evolution of this type of nevus: the globular and starburst pattern are typical of the growth phase and the homogeneous or reticular pattern appears when the lesion becomes stable. In a recent study by Argenziano *et al*., authors followed a series of 64 lesions in pediatric patients (mean age: 10.4 years) for a mean follow-up period of 25 months. In this study, 79.7% (n = 51) of lesions showed an involution pattern and 20.3% (n = 13) showed a growing (n = 4) or stable pattern (n = 9). The great majority of growing lesions were pigmented or partially pigmented (92.3%), whereas 47.1% of lesions in involution were amelanotic (p = 0.005) [99].

Histopathologically, classic Spitz nevi reveal neat organizational attributes such as symmetry, maturation, distinct margins, small size, and more often show epidermal hyperplasia, Kamino bodies and junctional clefting.

Although, there is lack of consensus regarding management of Spitz tumors, some authors recommend surgical excision of all types of Spitzoid lesions at any age. However, because younger age is associated with a lower predictive probability for true melanoma, a conservative management can be reserved in this age group for classic Spitz/Reed nevi. Regular dermoscopic monitoring every 4 months until stabilization or involution of the lesions has been recently proposed as a method to monitor common Spitz/Reed nevi before puberty [100,101].

After puberty and in adulthood, excision of Spitzoid lesions is recommended, regardless of the atypical clinical and/or dermoscopic characteristics detectable.

Due to the lack of distinction criteria that permit distinguishing Spitz nevi from pyogenic granulomas, surgical excision and histopathologic examination are also recommended when lesions show features of pyogenic granuloma, independent of age (**Figure 6**) [102].

Atypical Spitz tumors

AST are melanocytic tumors characterized by 'bland' (low-grade) histopathologic features and a metastatic potential usually confined to regional lymph nodes [100]. Different clinical parameters have been used to differentiate classic Spitz nevi from AST. First of all, younger age (<10 years) is associated with more probably benign Spitz nevus; conversely, AST usually affect older ages (10–20 years) [100]. Location is another important parameter, with extremities being more likely affected by Spitz nevi, while the back is the main location of atypical Spitz nevi [100]. Lesions <5–6 mm in diameter are usually common in classic Spitz nevus, while lesions >1 cm are likely to be atypical [100]. Other features suggesting benignity are symmetry, well-defined borders, smooth surface and pink/reddish color [100]. Conversely, AST often present as asymmetric with irregular borders, ulcerated or irregular surface and not uniformly colored [100].

Upon dermoscopy, AST potentially show all the dermoscopic elements typical of melanoma. The presence of a blue-white veil, resulting from deep dermal pigmentation with overlying epidermal hyperplasia, can produce a further increase of dermoscopic atypia.

In clinical practice, childhood Spitz nevi must be excised if one of the following features is present: larger than 1 cm, nodular, ulcerated, rapidly changing or otherwise atypical [100].

To date, no adequate clinical and histopathologic criteria exist to correctly classify these lesions. Ulceration, significant Breslow thickness, a high number of mitotic figures, even more if deep and atypical, may be associated with metastatic behavior [100]. A recent work by Spatz *et al*. established several clinical and histopathological parameters (assigning to each one a score) to define three different risk categories of developing metastases: low, intermediate and high [103]. However, most histopathological criteria are not useful when there is a doubtful overlap between AST and melanoma.

As a consequence, the management of AST is a matter of ongoing discussion. It was suggested by Kelley and Cockerell [104] in 2000 that sentinel lymph node (SLN) biopsy should be performed along with wide excision for patients with AST. Lymph node positivity for metastatic tumor deposits would be the supporting element in favor of the malignant nature of the primary tumor [104]. The full biologic and prognostic significance of a positive SLN discovered with AST is unclear. Nearly all of the reported SLN-positive cases yielded negative nodes after lymphadenectomy [101]. In addition, almost none led to death in the subsequent 1- to

3-year follow-up period [105,106]. There is no consensus on this matter and no outcome data exist with AST documenting a survival benefit with SLN biopsy. These data, moreover, also indicate that the prognostic value of SLN biopsy in AST in children is very limited [101].

The main problem related to positive SLN in AST is that it induces a chain of events, including extensive lymphadenectomy and eventual adjuvant treatments. Both procedures are associated with many adverse effects and do not benefit patient survival. Luo *et al*. defined this condition in a highly provocative way: 'benign metastasis' [101]. The question still remains open and AST represent a unique avenue in cancer research.

Genetic differences between Spitz nevus and melanoma have been studied through several molecular-biology techniques such as comparative genomic hybridization, loss of heterozygosity analysis, multiplex ligation-dependent probe amplification and DNA sequencing [107–114].

A subset of Spitz tumors has been found to show, with comparative genomic hybridization, amplifications in chromosome 11p (containing the *HRAS* gene), which represent a unique chromosomal aberration not commonly detectable in melanoma [115]. These Spitz tumors with 11p amplifications share histological features with melanomas.

Initial reports showed that Spitz nevi do not typically contain *BRAF* and *NRAS* mutations, commonly found in other types of melanocytic nevi and melanoma, including Spitzoid melanoma (SM) [109,116–119]. The thrilling result has been recently challenged when mutations in *BRAF* (5–20%) and *NRAS* (0–5%) were also demonstrated in classic Spitz nevi (Figure 7) [120–122].

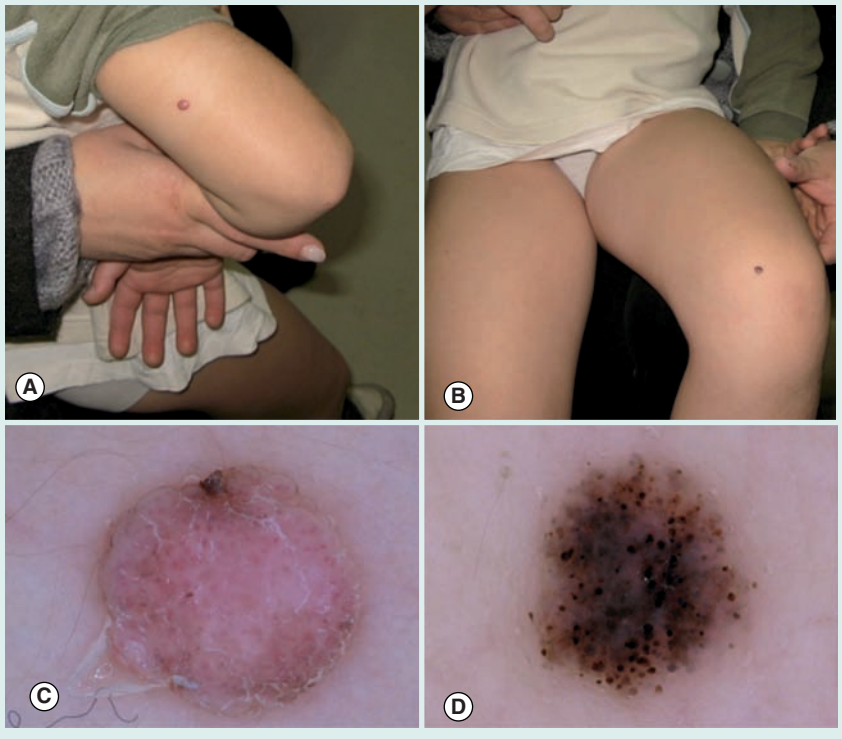

Figure 6. Clinical images of a Spitz and Reed nevus. (A) A Spitz and **(B)** a Reed nevus arising, respectively, as a pink and black papule on the upper and lower arm of a 3-year-old boy. **(C)** Dermoscopy of nonpigmented Spitz nevus with dotted vessels and pinkish background. **(D)** Dermoscopy of Reed nevus, showing a globular pattern, composed by heavily pigmented brown-to-black globules.

Melanoma

Melanoma, although relatively rare in children, accounts for 1–3% of childhood malignancies [1]. Children and adolescents (0–17 years of age) have accounted for only 1.3% of the cases of cutaneous melanoma in the USA during the past two decades [123], 79% occurring in adolescents [124] and only 0.3–0.4% during the first decade of life [125]. The estimated annual incidence of disease in children and adolescents younger than 15 years is approximately one per million [126,127].

An increase of incidence in childhood melanoma has been indicated by recent reports [126,127], but lack of agreement still exists, because of different age groups considered in the different studies [3]. If considering postpubertal age, an actual rise in incidence of melanoma is registered, whereas no increase has been reported for children younger than 10 years [3]. In fact, childhood melanoma incidence increased 2.9% per year in the period from 1973 to 2001 [128] and, it is seven-times more frequent in children aged >10 years than in first decade of life.

In both children and adults, risk factors for melanoma development are: intermittent and intense sun exposure, history of sunburns, tendency for freckling, fair skin, blue or green eyes and blond or red hair [128]. In childhood, one can consider further additional risk factors including xeroderma pigmentosum, giant CMN, high nevus count, presence of atypical nevi or many acquired melanocytic nevi, family history of melanoma and immunosuppression [128].

Giant CMN, among the aforementioned risk factors, represent the most important [16]. In fact, approximately a third of all melanomas before the age of 12 years derive from pre-existing giant CMN [10,16] and they often have a bad prognosis (70% of deaths). Nevertheless, the possibility of melanoma development from CMN is low (0.7%) [16].

Recently, an extensive review on melanoma occurring in patients younger than 20 years showed that about 18 deaths per year were detected in the USA in the period from 1969 to 2004 with a total of 643 deaths [16,129]. Calculating the overall age-adjusted mortality rate of childhood melanoma, it resulted in 2.25 deaths per year [16]. It is interesting to observe how the mortality was age-related, being from eight- to 18-times higher after puberty with about 20% of deaths occurring before 14 years of age [16]. Mortality rate for melanoma in childhood has progressively

decreased between 1968 and 2004 [16,130]. Childhood melanoma shows a higher thickness than adult type [130], a higher prevalence of positive regional lymph nodes, but a better prognosis if considering the overall survival in adult melanoma with the same features [6,130,131]. Some argue that the different behaviors of melanoma in childhood could also be related to misdiagnosis, as in several histopathologic studies, lesions initially diagnosed as melanoma were reclassified as Spitz nevi/tumors when reviewed retrospectively [1,4–6]. Paradela *et al.* have compared the prognosis of SM and non-SM in pediatric patients (under the age of 18 years) [132]. Although the authors found that SM have poorer prognostic factors (higher Breslow thickness and mitotic rate, vertical growth phase, nodal metastases), they found a lower mortality rate in SM group (5.9%) than non-SM group (12%). This less aggressive behavior could be due to lower potential for widespread distant metastases of SM as compared with conventional melanomas or to the younger age of children with SM. Of note, authors did not include all the lesions for which a definite diagnosis between AST and SM was not possible [132].

Because of the exceptional occurrence of melanoma in childhood, there are no accurate and detailed clinical or dermoscopic criteria to define it. Pediatric melanoma usually lacks features of the classical pigmented melanoma; it often presents as an amelanotic and nodular lesion, more similar to a pyogenic granuloma or nonpigmented Spitz nevus. In these cases, the clinical EFG (E = elevation; F = firm on palpation; G = growing progressively for more than a month) rule may be helpful in summarizing the clinical symptoms of such melanomas. The most frequent dermoscopic pattern observed in amelanotic melanoma is a polymorphous pattern composed of a combination of dotted vessels and linear, irregular vessels often associated with remnants of pigmentation. Less frequent features, but highly specific for nodular amelanotic melanoma, are milky-red globules characterized by a red–white color, irregular size and blurred borders. The most frequent dermoscopic pattern observed in pigmented melanoma is a multicomponent pattern.

Melanoma appearing in the context of a CMN presents as a growing nodular lesion within the pre-existing nevus. Early detection of changes, and also before the appearance of nodules, is possible with periodic dermoscopic examination of CMN. As a general rule, a biopsy should be performed either on a growing amelanotic nodule or when a recent and sudden change is detected by clinical or dermoscopic examination [16].

The management of childhood melanoma does not differ from that in adults. Early detection remains the mainstay in the treatment to assure a favorable prognosis. If a suspected lesion is detected, narrow margin excision with a request for expert histopathologic diagnosis is recommended. If confirmed, re-excision with adequate margins is warranted. The role of SLN biopsy as a prognostic method in childhood melanoma requires future clarification and should be considered critically. After surgical removal, regular follow-up visits according to established protocols should be performed.

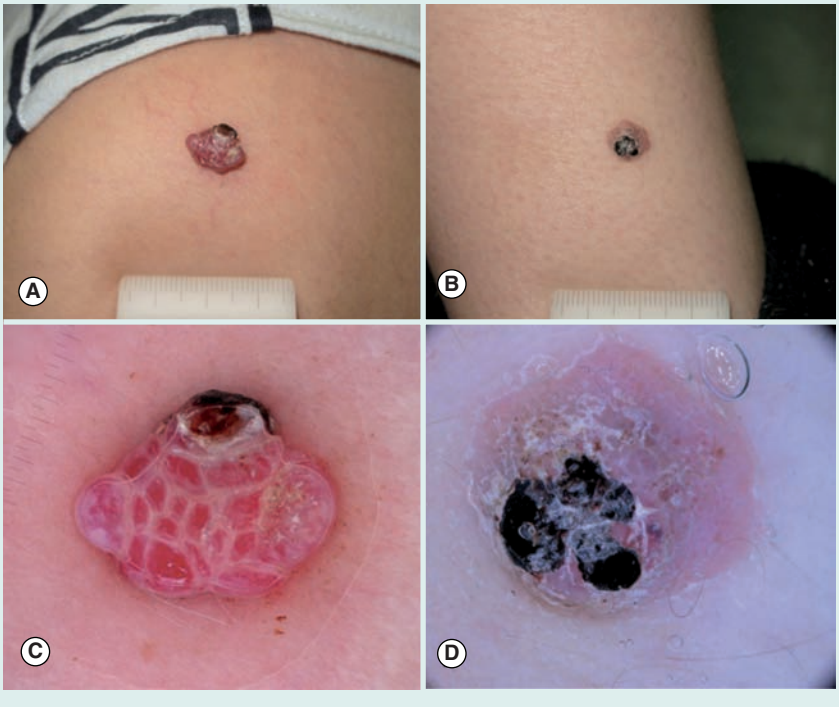

Figure 7. Clinical images of a pyogenic granuloma and an atypical Spitz tumor. **(A)** A pyogenic granuloma and **(B)** an atypical Spitz tumor arising on the lower arm of two prepubertal children. Both lesions presented as pink to red nodules, partially covered by a blood crust. **(C)** Dermoscopy of pyogenic granuloma, displaying multiple red lacunes intersected by whitish lines. In the upper part of the lesion, a small ulcerated area is visible. **(D)** Aspecific dermoscopic pattern of an atypical Spitz tumor presenting a pink background with a few dotted vessels and a keratotic surface partially covered by a blood crust.

Expert commentary

Childhood melanoma is extremely rare, and in the great majority of cases, melanocytic lesions in childhood are benign and can be managed conservatively. Nevertheless, accuracy in melanoma detection in children and adolescents still remains low, and a high proportion of benign lesions are excised in order to rule out melanoma. An effective strategy to reduce unnecessary excision without overlooking melanoma would be to focus on problematic lesions. Congenital nevi and Spitz/Reed nevi are the most problematic lesions in differential diagnosis with melanoma in childhood. The risk of melanoma associated with CMN is related to the nevus size and particular attention should be paid to giant CMN, especially in younger age. However, since the risk of melanoma development within CMN seems to be less than 1%, the question is raised of which the best and most reasonable management of giant CMN is: excision in young age or,

alternatively, periodic clinical and dermoscopic monitoring. One more cause of concern in very young children with CMN is the risk of developing NCM, a melanocytic proliferation of the CNS that may provoke intracranial hypertension. Children affected with symptomatic NCM usually have a scarce prognosis, therefore a neurological consultation could be very helpful for early detection of precocious disease manifestations.

Spitz/Reed nevi appearing before puberty are simply recognized and managed conservatively when <1 cm sized and showing no clinical and dermoscopic atypia. Conversely, for Spitzoid lesions of childhood and adolescence presenting as larger than 1 cm, nodular, ulcerated or rapidly changing, excision must be considered. Due to the lack of identification criteria that permit the distinguishing of Spitz nevi from pyogenic granulomas, surgical excision and histopathologic examination are also recommended.

Overlapping features with melanoma may be occasionally shown by Spitz nevi. Although rare, it is conceivable to find Spitzoid lesions diagnosed as malignant only retrospectively (i.e., after the appearance of metastases). Conversely, it has been demonstrated that some childhood melanomas were re-evaluated and retrospectively diagnosed as Spitz nevi. Wide excision is mandatory in Spitzoid lesions with atypical histopathologic features and the decision of performing SLN biopsy should be individually considered. The location of the lesion has to be taken into account and parents should be aware that this procedure has not been proven to give a survival benefit and it may carry a risk of iatrogenic morbidity.

In conclusion, as a general rule to exclude childhood melanoma, a biopsy should be always performed when, within a CMN, a growing amelanotic nodule appears or a change is discovered clinically, and especially dermoscopically.

Five-year view

Future studies investigating the natural evolution of melanocytic nevi in children are needed. A better knowledge of the natural history of nevi in this age group would probably allow a better management of pediatric patients, leading to a decrease in the number of unnecessary excisions of benign lesions. In this field, a better understanding of the biology of Spitzoid lesions is mandatory in improving the clinical management of these neoplasms. Spitzoid lesions seem to be a particular subgroup of melanocytic proliferations that show a malignant morphology but a relatively benign biological behavior. They can sometimes be morphologically indistinguishable from melanoma but follow a benign clinical course. To date, there is still a spectrum of Spitzoid neoplasm cases for which morphology cannot predict biology of the tumor. Further research is needed that will probably include new findings from molecular biology, in order to better classify and finally manage these lesions.

Key issues

- Melanocytic lesions in children are managed conservatively in the great majority of cases.
- Large congenital melanocytic nevi (CMN) and Spitzoid lesions are the main problematic lesions in children.
- The risk of melanoma associated with CMN is proportional to the nevus size; however, less than 1% of children with congenital nevi will develop melanoma, thus regular clinical and dermoscopic follow-up can represent a reasonable management option.
- The risk of neurocutaneous melanocytosis should be taken into account in children with giant CMN, and a high number of satellite lesions. This condition represents a proliferation of melanocytes within the CNS and may have a very poor prognosis due to the risk of increased intracranial pressure.
- Classical or pigmented Spitz nevi of prepubertal age can be easily recognized and managed conservatively with periodic clinical and dermoscopic evaluation.
- Large (>1 cm), nodular, ulcerated, rapidly changing, atypical Spitz lesions in childhood must be excised.

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Analysis of clinical and dermoscopic features in melanocytic lesions with special emphasis on problematic lesions in children

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing a 12-year-old healthy girl with several melanocytic skin lesions that her parents have noticed for either months or years. They are concerned regarding her risk of skin cancer. Which of the following types of skin lesions are most associated with the diagnosis of melanoma among children?
   - ☐ **A** Blue nevi and combined nevi
   - ☐ **B** Congenital melanocytic nevi (CMN) and Spitz nevi
   - ☐ **C** Halo nevi and combined nevi
   - ☐ **D** CMN and blue nevi

2. The patient has several benign-appearing skin lesions. Which of the following statements regarding low-risk melanocytic nevi among children is most accurate?
   - ☐ **A** The globular pattern is most common on dermoscopy
   - ☐ **B** Blue nevi are generally flat
   - ☐ **C** Halo nevi are usually found on the arms and legs
   - ☐ **D** Even benign-appearing nevi on the palms and soles should be excised

3. The patient also has a CMN on her back with a diameter of 22 cm. What should you consider regarding the clinical features and management of this lesion?
   - ☐ **A** The risk of developing melanoma in this giant CMN is less than 0.01%
   - ☐ **B** Nodules originating from large CMN are typically easy to differentiate from melanoma
   - ☐ **C** She is a good candidate for dermoabrasion
   - ☐ **D** Early recognition of malignant melanoma is very difficult in cases of giant CMN

4. The patient also has a flesh-colored nodule on her thigh, which appears to be a Spitz nevus. What should you consider regarding these nevi?
   - ☐ **A** They are rich in melanin
   - ☐ **B** Atypical Spitz tumors (AST) are more frequent in children less than 10 years of age vs adolescents
   - ☐ **C** AST can demonstrate the same features as melanoma on dermoscopy
   - ☐ **D** Excision of spitzoid lesions is unnecessary among most adolescents