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REVIEW ARTICLE

Congenital melanocytic naevi: An up-to-date overview

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ABSTRACT

Congenital melanocytic naevi are hamartomas of the neuroectoderm caused by genetic mosaicism. Congenital melanocytic naevi are seen in 1-6% of all live births and commonly classified based on the projected size in adults. Congenital melanocytic naevi appear in different colours, shapes, and sizes, and occasionally present with complications. In this review, we sought to evaluate congenital melanocytic naevi, their clinical, dermatoscopic, and reflectance confocal microscopic features, behavioural pattern over time, new trends in classification, underlying genetic factors and their influence on clinical manifestations and management, associated risks, complications, magnetic resonance imaging findings and their management in the light of recent literature.

Key words: classification, congenital melanocytic naevi, dermatoscopy, dermoscopy, follow-up, genetics, management, neurocutaneous melanocytosis, reflectance confocal microscopy, surgery, treatment.

INTRODUCTION

Congenital melanocytic naevi are hamartomas of the neuroectoderm caused by genetic mosaicism. Although CMN is a well-established condition, recent studies have focused on improvement of classification, identification of underlying genetic mechanisms, new treatment options, experimental therapies, and new insight to management of the disease.

In this article, we aimed to review the pathogenesis, clinical features, and associated complications with respect to CMN as well as updates on CMN classification, changes in clinical practice and management, experimental therapeutic approaches, and future implications.

MATERIALS AND METHODS

We reviewed the medical literature (PubMed and Ovid Medline databases) on August 2020, using Mesh key terms: 'congenital melanocytic naevi/naevus, neurocutaneous melanocytosis/melanosis, genetics, classification, treatment, melanoma, dermoscopy, dermatoscopy, reflectance confocal microscopy, surgery, lasers' to identify the case reports, case series, studies and review articles about CMN. Further papers were also identified from the reference lists of the above retrieved papers and citations. Our search included articles in the English-language, published between 1981 and 2020. The selection process included first the screening of titles and abstracts and then the evaluation of the full text articles.

EVOLUTION OF CONGENITAL MELANOCYTIC NAEVI

Congenital melanocytic naevi (CMN) are hamartomas of the neuroectoderm, often being present at birth. There is a growing opinion that majority of CMN appear within the first few years of life, these being referred to as tardive congenital naevus. These tardive congenital naevi, sometimes but not always, are characterised by the presence of terminal hair as a clue to their hamartomatous origin.[1]

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Other compound naevi on these patients often have a similar clinical and histological morphology, including peri-adnexal proliferation of melanocytes.[2]

CMN are comprised of a clonal proliferation and migration of neural crest melanocytes caused primarily by mutations in NRAS[3] and occasionally in BRAF[4] oncogenes and are seen in 1-6% of all live births.[5] Large/giant CMN occur in 1/20,000-500,000 births and are usually associated with other smaller CMN.[6]

CMN appear as flat tan or brown macules or papules and tend to become thicker and mamillated with well-demarcated, round borders as they grow. The morphology of CMN is heterogenous with the lesions occurring in varied sizes, shapes, and colours. The lesions exhibit a gradual and proportional increase in size with advancing age (by a factor of 2.8, 8 and 12 in head, trunk, and arms-legs respectively) and may tend to become plaque like or nodular.[7] The CMN become lighter and hairy as child grows. A recent study by *Kinsler et al*., showed that the final colour of the CMN is related to underlying skin tone of the baby. In light-skinned individuals, final colour of CMN tends to be lighter in contrast to the lesions in dark skinned individuals.[8] Sometimes CMN can have a halo around it and there may be eventual lightening of the naevi, even of large/giant naevi. Vitiliginous lesions are seen on other parts of the body in one third of the affected individuals with halo phenomenon.[6]

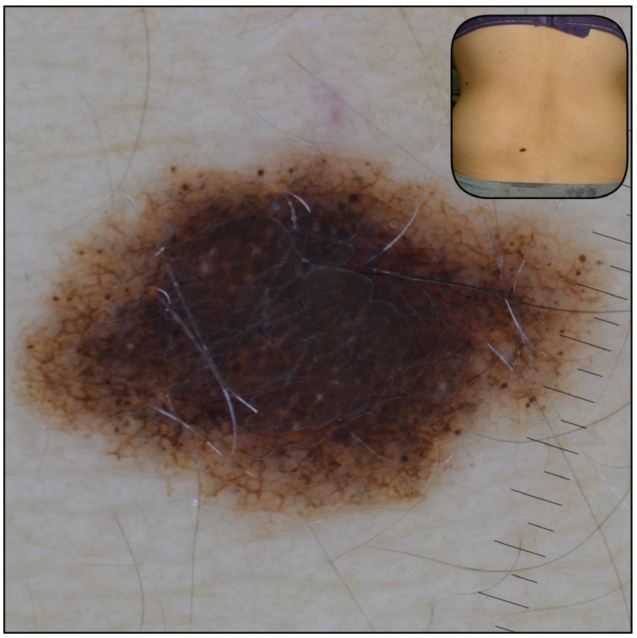

Figure 1 Small-sized congenital melanocytic naevus. The dermatoscopic image shows a symmetrical lesion with central homogenous pigmentation with a papillomatous surface, terminal hairs, a uniform peripheral reticulo-globular pattern, and peripheral brown clods.

CLASSIFICATION, PATTERNING AND DISTRIBUTION OF CONGENITAL MELANOCYTIC NAEVI

For many decades, CMN have been classified based on the projected adult size of the lesions and this is the most common classification used today. Categories of CMN according to the estimated diameter in adulthood include small (smaller than 1.5 cm) (Fig. 1), medium (1.5-20 cm) (Fig. 2) and large (larger than 20 cm) (Fig. 3). CMN with a projected adult size of 40 cm or larger are classified as giant.[7] The main drawback with this classification is that it considers only the size of the lesions to project the risk of melanoma, without giving any consideration towards other features of CMN. Additionally, the risk of melanoma arising from CMN is not proportional to size as a linear metric, however, it is known to be higher in CMN over 20 cm in adult size.[9] Recent studies have estimated a high lifetime melanoma development risk in giant CMN and CMN which accompanied by multiple smaller CMN.[10-12] There are few studies dealing exclusively with giant CMN and its relation to melanoma.[9,12,13] Although giant CMN is considered a risk factor for the development of melanoma, the real incidence of malignancy is still a controversy.[14] The risk of developing melanoma over a CMN varies from 0 to 4.9% for small and medium naevi[15] and from 1 to 31% for giant naevus.[16] In 2013 *Krengel et al*. proposed a new classification for CMN, which included other parameters like rugosity (R0: none, R1: moderate, R2: marked surface rugosity), colour (C0: none, C1: moderate, C2: marked colour heterogeneity), nodularity (N0: none, N1: scattered, N2: extensive dermal or subcutaneous nodules), presence of hair (H0: none, H1: notable, H2: marked hypertrichosis), satellite lesions (no satellites, <20, 20-50, 50<), and location, in addition to the diameter of the lesion (Table 1). A moderate to excellent interobserver agreement for the classification of CMN has been achieved with these parameters and the authors concluded that this new classification facilitated uniform interpretation enabling better clinical management and outcomes.[17]

CMN have also been classified based on the site and pattern of occurrence on the body such as bathing trunk, vest-like, cape-like, stocking-like, Blaschkoid, flag-like etc. in the past.[18]

More recently, *Martins da Silva et al*., proposed a new system of classification for giant CMN, called the 6B rule. In this method, the authors assorted patients into different categories such as bolero, back, bathing trunk, breast/belly, body extremity (Fig. 4) and body type.[19] Another classification of CMN has been proposed by *Kinsler et al.* This classification system is based on the migration of precursor melanocytes from the dorsal midline, in a non-segmental pattern, at the time of gastrulation during embryogenesis.[20] In another classification system, authors have classified CMN based on the timing of events in embryological development.[21] Streamline classification may be useful as a research tool and help to identify high-risk CMN lesions and prevent its complications.

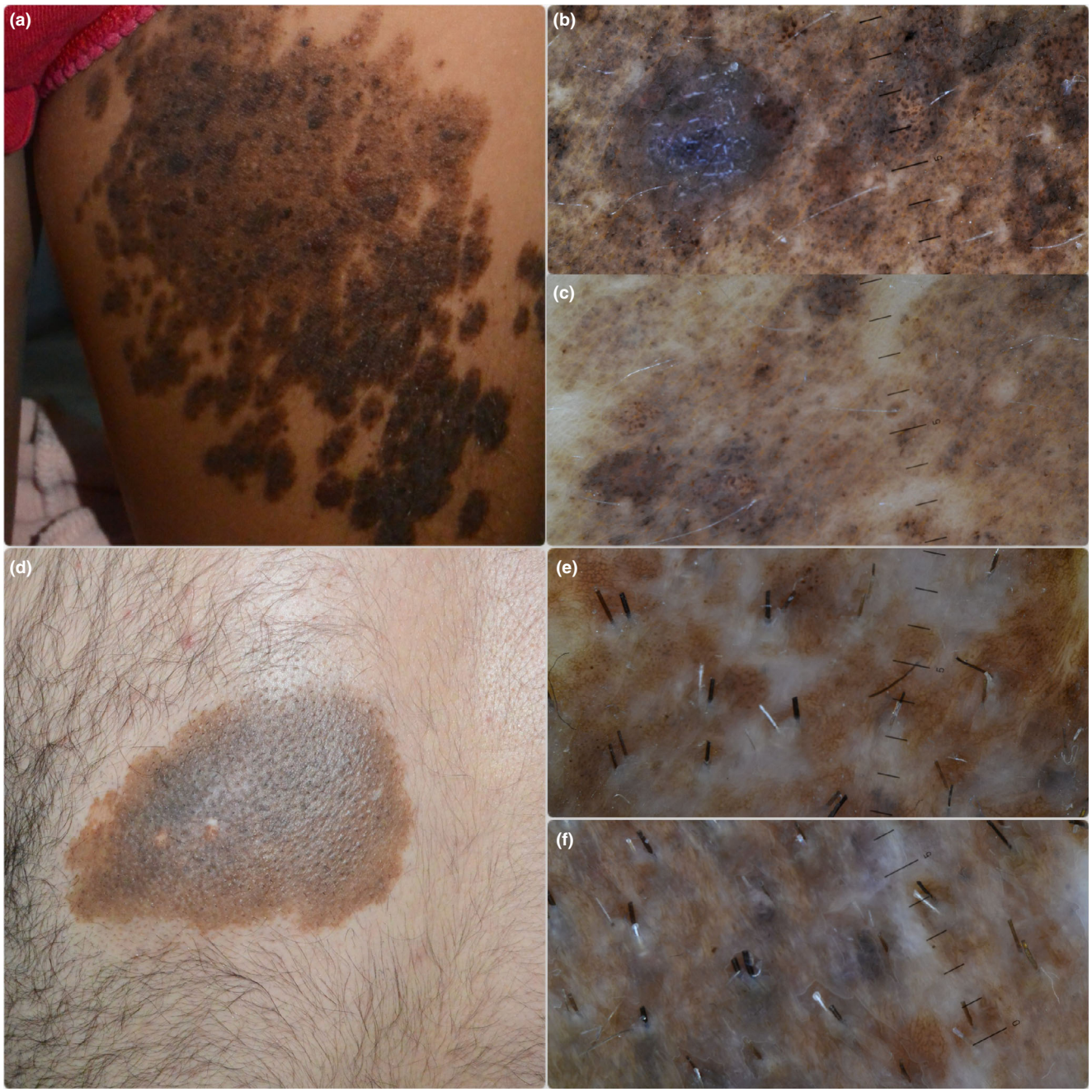

Figure 2 Examples of medium-sized congenital melanocytic naevi. (a) A medium-sized CMN located on the left flank of a 6-year-old female patient. (b, c) The dermatoscopic images show perifollicular hypopigmentation, atypical network, blotches, crystalline structures. (d) A medium-sized CMN located on the left flank of a 32-year-old male patient. (e, f) The dermatoscopic images show numerous terminal hairs and perifollicular hypopigmentation and interfollicular regular reticular network.

GENETICS OF CONGENITAL MELANOCYTIC NAEVI

CMN occur due to genetic mosaicism. Mosaicism refers to the occurrence of two or more different cell populations in the same person as a result of post-zygotic mutations. If these mutations occur in early stages of foetal life, lesions tend to be more extensive.[22]

Genetic studies showed a tendency towards mutations in BRAF oncogene in small CMN lesions, whereas, NRAS mutations tend to be seen in large/giant CMN.[23] A recent study revealed the presence of NRAS gene (codon 61)

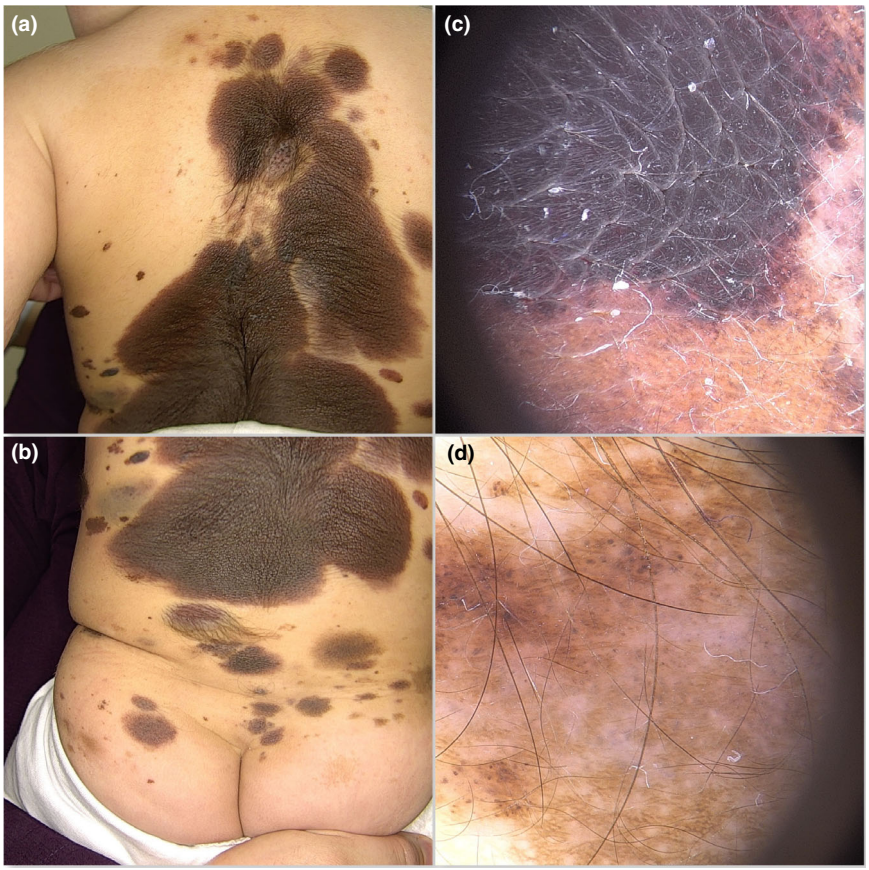

Figure 3 Large-sized congenital melanocytic naevus located on axial location, showing multiple satellite lesions. The dermatoscopic images show homogenous black structureless elevated part, perifollicular hypopigmentation, globules, atypical network, terminal hairs

mutations in multiple CMN and concurrently occurring neurological lesions, but similar mutations were not seen in the individual's blood or unaffected tissue sites. These findings supported the hypothesis that the pattern of inheritance is not Mendelian and that CMN occur as a result of post-zygotic mutations.[24]

Salgado et al. conducted a prospective study to analyse genetic mutations in CMN. Sixty-six patients enrolled in this study were analysed for NRAS codon 61 mutations, negative cases being evaluated for BRAF V600E mutations. An NRAS mutation was detected in 51 (77.3%) and a BRAF mutation in 5 (7.6%) of the patients.[4] In contrast to other studies showing that BRAF mutations were mostly detected in small to medium-sized CMN,[3,25] BRAF mutations were detected only in large and giant CMN in this study, and two of the patients were diagnosed with neurocutaneous melanocytosis (NCM). From the clinical point of view, BRAF positive lesions were more nodular and less hairy compared to NRAS positive lesions. The authors concluded that BRAF V600E is also associated with large/giant CMN and NCM, and these findings open a possibility of BRAF-targeted therapy in selected cases in the future.[4]

In some cases, no mutations in the genes examined were found in CMN.[24] One report described a patient with multiple CMN who died of metastatic disease at 5 months old, but no BRAF or NRAS mutation identified in spite of multiple biopsies.[26]

NEUROCUTANEOUS MELANOCYTOSIS OR CONGENITAL MELANOCYTIC NAEVI SYNDROME

Neurocutaneous melanocytosis is characterised by multiple CMN or single giant naevi associated with benign or malignant, diffuse, or localised melanocytic proliferations in the leptomeninges and/or brain parenchyma.[27] Most of the patients with NCM are asymptomatic,[28] however, patients with large/giant CMN in a posterior axial location are prone to develop symptoms, especially when the CMN are associated with multiple satellite lesions.[29]

NCM may become symptomatic when the lesion exerts a mass effect on the brain cells resulting in seizures, cranial/spinal nerve dysfunction, sensorimotor deficits, and bowel/bladder dysfunction. Patients may experience headache, recurrent vomiting, lethargy, photophobia and hydrocephalus due to increased intracranial pressure.[30]

Symptoms of NCM generally appear before the age of two,[31] however delayed presentation in older children, adolescents and adults has also been reported, usually

Table 1 Proposed new classification of congenital melanocytic naevi by Krengel et al[12]

CMN parameter	Terminology	Definition
CMN projected adult size	Small CMN	<1.5 cm
	Medium CMN	
	'M1'	1.5-10 cm
	'M2'	>10-20 cm
	Large CMN	
	'L1'	20-30 cm
	'L2'	30-40cm
	Giant CMN	
	'G1'	40-60 cm
	'G2'	>60 cm
	'Multiple medium CMN'	≥ 3 medium CMN without a single, predominant CMN
CMN localisation		
CMN of head	'Face', 'Scalp'	
CMN of trunk	'Neck', 'shoulder', 'upper back', 'middle back', 'lower back', 'breast/ chest', 'abdomen', 'flank', 'gluteal region', 'genital region'	
CMN of extremities	'Upper arm', 'forearm', 'hand', 'thigh', 'lower leg', 'foot'	
Number of satellite naevi	'S0'	No satellites
	'S1'	<20 satellites
	'S2'	20-50 satellites
	'S3'	>50 satellites
Additional morphologic characteristics	'C0'	None
Colour heterogeneity	'C1'	Moderate
	'C2'	Marked colour heterogeneity
Rugosity	'R0'	None
	'R1'	Moderate
	'R2'	Marked surface rugosity
Nodularity	'N0'	None
	'N1'	Scattered
	'N2'	Extensive dermal and subcutaneous nodules
Hairiness	'H0'	None
	'H1'	Notable
	'H2'	Marked hypertrichosis

with mild symptoms such as headaches and neuropsychiatric manifestations.[32]

In 2012, *Kinsler et al.* proposed the name CMN syndrome instead of NCM. This description included patients with multiple CMN associated with extra-cutaneous manifestations including neurologic involvement (clinical or radiological) with characteristic facial features (wide or prominent forehead, hypertelorism, eyebrow variants, periorbital fullness, small/short nose, narrow nasal ridge, broad nasal tip, broad or round face, full cheeks, prominent premaxilla, prominent/long philtrum, and everted lower lip), and rare/subtle endocrine manifestations. This nomenclature implies a common terminology for all the patients with multiple CMN and associated systemic manifestations.[33]

In the past, NCM disease with any symptoms, portrayed a poor prognosis regardless of the CMN type. Treatment options were very limited for central nervous system (CNS) melanoma/progressive disease.[31] Recent studies have helped classify patients with CMN syndrome into 3 subtypes (1) intraparenchymal melanocytosis, the most common finding in magnetic resonance imaging (MRI), (2) leptomeningeal disease (diffuse/localised), and (3) CMN with other neurological abnormalities (developmental delay & learning disabilities, abnormal tone, Dandy-Walker/Arnold-Chiari malformation, lissencephaly, corpus callosum agenesis, CNS tumour-astrocytoma, choroid plexus papilloma, ependymoma or pineal germinoma).[34-36]

RADIOLOGIC EVALUATION IN CONGENITAL MELANOCYTIC NAEVI SYNDROME

Contrast enhanced MRI of the brain and spine is the investigation of choice in diagnosing CMN syndrome and ideally they should be performed within the first 4-6 months of life, before myelinisation occurs, because myelinisation of the brain obscures the melanin signal.[7] With the advanced techniques available now, the sensitivity of MRI can be increased even after 6 months.[37]

MRI can be used as a predictor of clinical outcome in patients with multiple CMN. In one study 21% of the patients with multiple CMN had a CNS abnormality. This study showed that MRI abnormalities are better predictors than adverse outcome measures of NCM (seizures, neurodevelopmental problems, requirement for neurosurgery, primary CNS melanoma) and clinical phenotype (size, location, number, and other features of CMN). The most observed abnormality on MRI was isolated intraparenchymal melanocytosis. The intraparenchymal melanocytosis group had a good prognosis regardless of the presence of neurological symptoms and was not associated with CNS melanoma or death. The leptomeningeal disease group had higher morbidity and risk of death due to CNS melanoma.[38] In the past, only patients with more than 20 satellite lesions or large/giant CMN (> 20 cm) at birth were screened for CNS abnormalities.[39] *Waelchi et al.* recommended baseline MRI screening of the brain/spine under the age of 12 months (ideally < 6 months) in patients with 2 or more CMN in any size or location. However, it is unclear if these approaches can be applied uniformly in broader health care systems.[38] Currently, MRI is recommended in patients with any neurologic symptoms and in asymptomatic patients with high risk for adverse outcomes (>20 satellites at births, larger size CMN > 40 cm, multiple medium-sized CMN).[37]

Referral for neurological, neurosurgical, and oncological evaluation may be required in symptomatic patients with positive MRI findings. Monitoring these children for developmental delay and neuropsychological evaluation and treatment (when indicated) is required. If there are

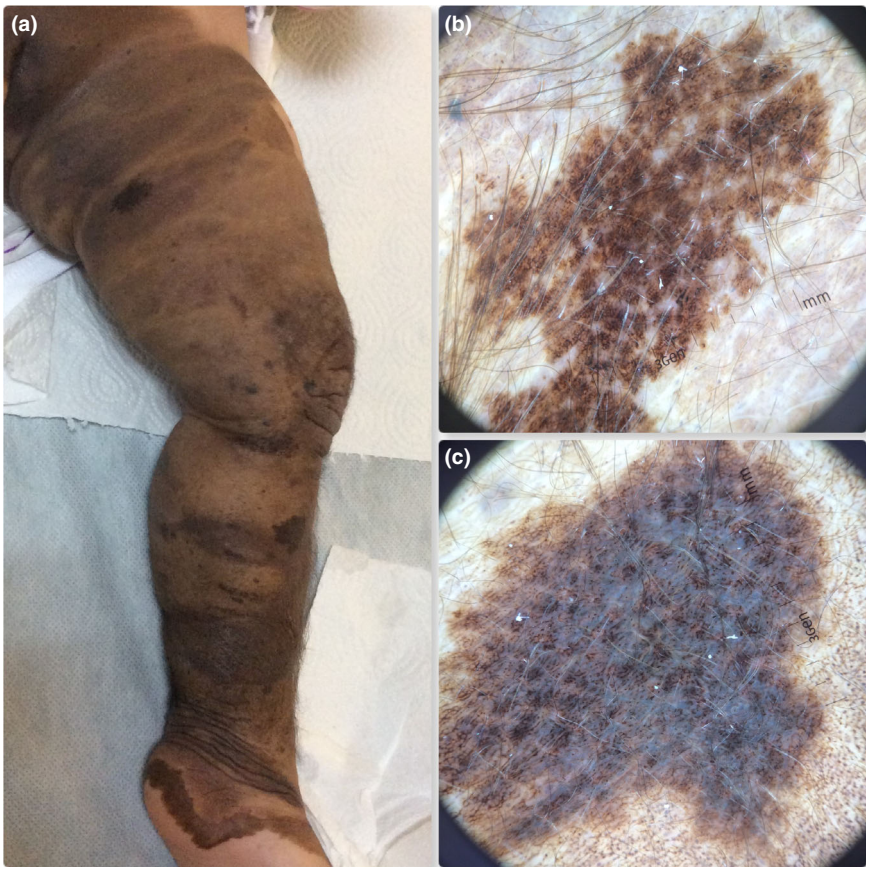

Figure 4 Large-sized congenital melanocytic naevus (Leg type). (a) A hyperpigmented brown lesion with heterogeneous pigmented areas on the lesion. (b) The upper dermatoscopic image shows an asymmetrical pigmented lesion with reticular network and perifollicular hypopigmentation. (c) The lower dermatoscopic image shows an asymmetrical pigmented lesion with central hyperpigmentation, grey-blue colour with peripheral reticular and globular network, and numerous terminal hairs.

positive MRI findings without any symptoms, referral for neurological evaluation is recommended, but monitoring with a follow-up MRI is not recommended until the child shows symptoms.[39]

MELANOMA RISK IN CONGENITAL MELANOCYTIC NAEVI

The overall risk of melanoma development in small and medium-sized CMN has been reported less than 1 %[10] and it occurs on the periphery of the lesion during adult life. Clinical and dermatoscopic features of melanoma arising from small/medium-sized CMN shows the same clinical and dermatoscopic features that are observed in sporadic melanomas, and histologically it usually originates from the dermo-epidermal junction.[10] Melanoma arising from these CMN mostly occurs at the leading edge of the naevus.[40] Considering the low risk of melanoma transformation in a single small or medium-sized CMN, removal of these lesions as a precautionary measure, in childhood/adolescence is not justified.

The risk of melanoma development in large/giant/multiple small to medium-sized CMN is less than 5%, and melanomas mostly originate from the dermis, but the exact risk is difficult to quantify.[41] Melanoma risk is higher particularly in lesions that lie across the spine or where there are multiple satellite lesions.[9,12] Melanoma development can start deep inside the naevus or within any NCM found in CNS.[42] Very rarely, other tissues that contain melanocytes may also be a source of melanoma, such as gastrointestinal mucosa and retroperitoneum.[28,42,43] In 24% of the cases, the origin of the melanoma cannot be identified.[44]

Melanoma associated with giant CMN can be very difficult to detect and treat. The risk of melanoma development is greater in early childhood; 70% of melanomas associated with giant CMN are diagnosed by the age of ten years.[10]

Unfortunately, when a rare melanoma arises within a giant congenital melanocytic naevus, the prognosis is unfavourable.[45] This is because the cutaneous melanoma associated with giant CMN typically grows in the dermis makes it more difficult to detect.[46] Rapid change and ulceration in congenital naevus are markers for the melanoma development.[14,47] Additionally, the rough, hairy, nodular surface of CMN masks the early observation of the tumour.[45]

The deeper location also facilitates earlier spread through lymphoid vessels and blood vessels of greater calibre, leading to early metastasis.[45] In 24% of cases, the melanoma has already metastases at the time of the diagnosis.[44]

One out of three melanomas develop primarily in the CNS in these patients, hence removing the CMN does not prevent the risk of death due to melanoma. In addition, patients with multiple CMN who also have abnormal initial MRI findings are at high risk for developing melanomas.[48] In one study, melanoma risk in patients with CNS abnormalities was reported as 12% compared to 1-2% in patients with normal MRI findings.[11] An example of CNS melanoma arising on occipital region of the scalp is given in Figure 5.

Treatment regimens have not been very effective in patients with CNS melanoma and targeted therapies might be helpful in these individuals.[49] Interestingly, using MEK inhibitors showed improvement in symptoms in children with NRAS driven-CNS melanoma and prolonged the life span of the affected children.[50] These findings were substantiated by experimental studies, which showed reduced viability of nevospheres present in neurocutaneous melanocytosis, when treated with specific inhibitors of NRAS signalling pathway.[51]

Besides from experimental studies, cutaneous melanoma arising on CMN is primarily treated surgically, and immunotherapy is a useful choice for metastatic disease.[52]

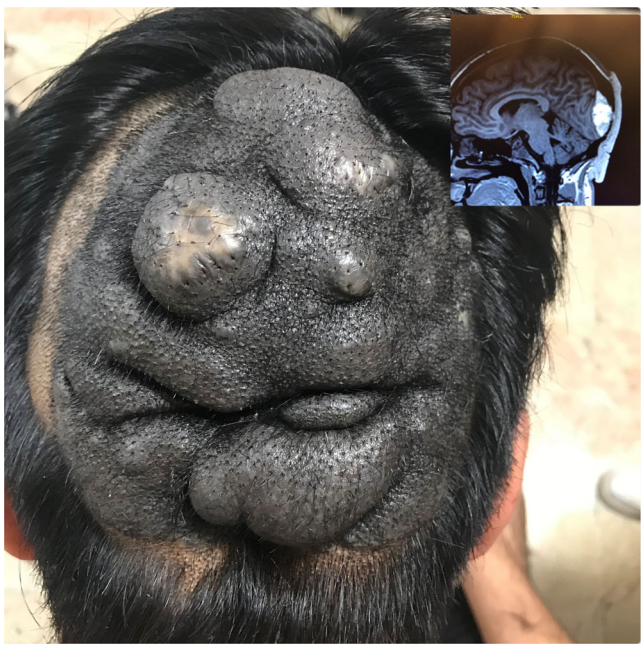

Figure 5 A large-sized CMN located on the occipital scalp of a 20-year-old male. The lesion shows a multinodular component with hypopigmented areas. Cranial MRI venography images reveal a melanocytic lesion with an exophytic component in the occipital scalp with diffuse cutaneous and subcutaneous tissue involvement. The patient has been diagnosed with CNS melanoma with extra-axial melanoma metastasis.

OTHER TUMOURAL DEVELOPMENTS ON CONGENITAL MELANOCYTIC NAEVI

There are other malignant tumoural developments described on large CMN including rhabdomyosarcoma,[53] liposarcoma,[54] undifferentiated spindle cell cancer,[54] malignant peripheral nerve sheath tumour[53] and neuroblastoma.[55] CMN may also be associated with benign tumours such as hemangiomas,[56] lipomas,[57] schwannoma[58] and proliferative nodules.[59]

Proliferative nodules are benign lesions that develop within generally large/giant CMN, arising within the first year of life, although, they can also be seen at birth. Little is known about epigenetic events that may drive the growth of PN in CMN. Proliferative nodule (PN) in giant CMN prevalence has been reported between 2.9 to 19%.[60-62] These lesions appear as smooth-surfaced, brown to black papules/nodules, often less than 1 cm in diameter, however, larger variants can be seen.[63,64] Occasionally, they can become ulcerated.[65] PNs are characterised by increased cellularity and large melanocytes in the background of CMN. PN are typically solitary, sometimes satellites or multifocal lesions can be seen.[66] Rapid growth, ulceration and haemorrhage can heighten the clinical concern for melanoma.[67] PN usually spontaneously regress, some of them remain stable over a prolonged period, exhibit enlargement and hyperpigmentation.[68]

Distinction between PN and melanoma be challenging, particularly PN with brisk mitotic activity in histopathology. Recent studies have shown that CGH/FISH studies[69,70] and specific immunohistochemistry marker (H3K27me3-an epigenetic gene silencer)[71] can be used for distinguishing PN versus melanomas developing in the background of CMN in childhood.

APPROACH TO CONGENITAL MELANOCYTIC NAEVI

The first step in making a correct diagnosis of CMN involves a complete medical history and a full-body physical examination. Naevus classification is important for prediction of melanoma risk in these patients. Additionally, assessment of hearing functions and visual acuity is recommended in patients with large-giant CMN since related structures can also be involved due to common embryological origin.[72] Also, contrast enhanced MRI of the brain/spine may be required for patients with large/giant or multiple small to medium-sized CMN. Developmental assessment and neurological examination are recommended in all patients with neurological symptoms or with positive MRI findings in the absence of any symptoms.[38]

Palpation of the lesions to evaluate depth of involvement is essential especially for large/giant CMN, since melanoma development tends to occur in deeper tissues. Melanoma specific dermatoscopic features can be seen in melanomas arising on small/medium-sized CMN. However, changes in dermatoscopic findings may not be always a sign of malignancy because CMN can grow over

time and may present with atypical dermatoscopic features.[73]

Dermatoscopic evaluation of CMN commonly shows globular, reticular-globular, reticular, and homogenous pattern in different age groups. Globular pattern is seen in the first 2 decades, whereas reticular pattern is seen after 3rd and 4th decades.[74] In addition to these main patterns, hypertrichosis, cobblestone like globules, milia-like cysts, perifollicular pigmentary changes, atypical dots/globules, and asymmetry, diffuse background pigmentation, hyphae-like structures and multicomponent pattern have been reported.[75] CMN lesions exhibit a vascular pattern in 70% of the lesions.[76] Serial examinations and follow-up are required for these individuals, especially for those with large/giant and multiple CMN to detect melanomas in their earliest possible stages. Rapidly growing nodules, especially those which are adherent to the deeper structures and immobile, and ulceration of the lesions, should raise suspicion of melanoma development.

Cuevas et al. described dermatoscopic melanoma predictors in small/medium-sized CMN as peripheral location of suspicious area, negative network, grey angulated lines and atypical network in a recently published study.[77] Of the local dermatoscopic features, negative network was the post potent predictor of melanoma. An example of melanoma arising on medium-sized CMN is given in Figure 6.

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique that enables in vivo visualisation of the various depths of epidermis and papillary dermis in real time. RCM creates greyscale images, oriented in a horizontal plane (en face), which reveals cellular and morphological architecture of the lesions. A recent study by *Odorici et al.* showed that RCM features closely corresponds to histologic counterparts of CMN, and can be used as an auxiliary tool for observing dynamic changes within the naevus according to age groups.[74] RCM features of CMN of various depths of epidermis and papillary dermis are as follows [78]:

-Regular honeycomb pattern at the spinous/granular layer of the epidermis (Fig. 7a).

-Hyperpigmented (hyperrefractile) keratinocytes in the basal layer (Fig. 7b),

-Ring pattern (Fig. 7c), meshwork pattern (Fig. 7d), clod pattern (Fig. 7e), or multicomponent pattern (Fig. 7f), corneal cysts (large, round, highly refractive intra-epidermal

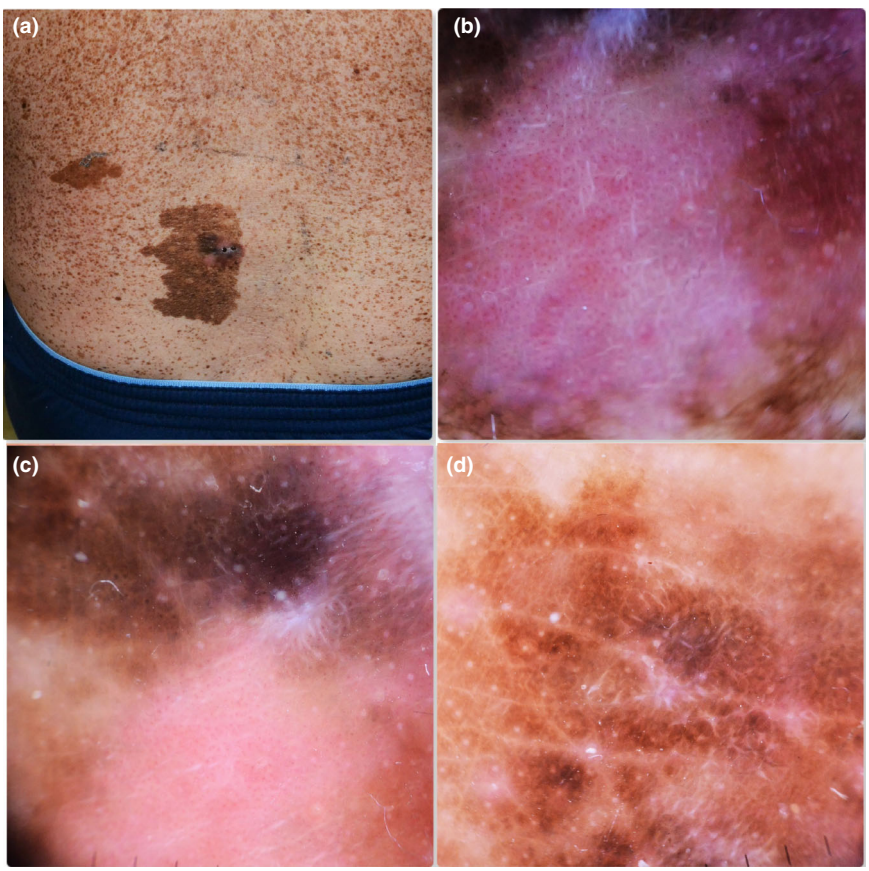

Figure 6 Melanoma arising on medium-sized CMN. A pigmented lesion with irregular borders 10 cm in diameter with a nodular component on the right middle part of the lesion (a). The dermatoscopic images show an atypical pigment network with prominent dotted vessels (b, c), prominent negative network with colour heterogeneity, atypical pigment network (d). Histopathologic examination of the lesion revealed a melanoma associated with a preexisting congenital type naevus, vertical growth phase with a 0.9 mm Breslow thickness.

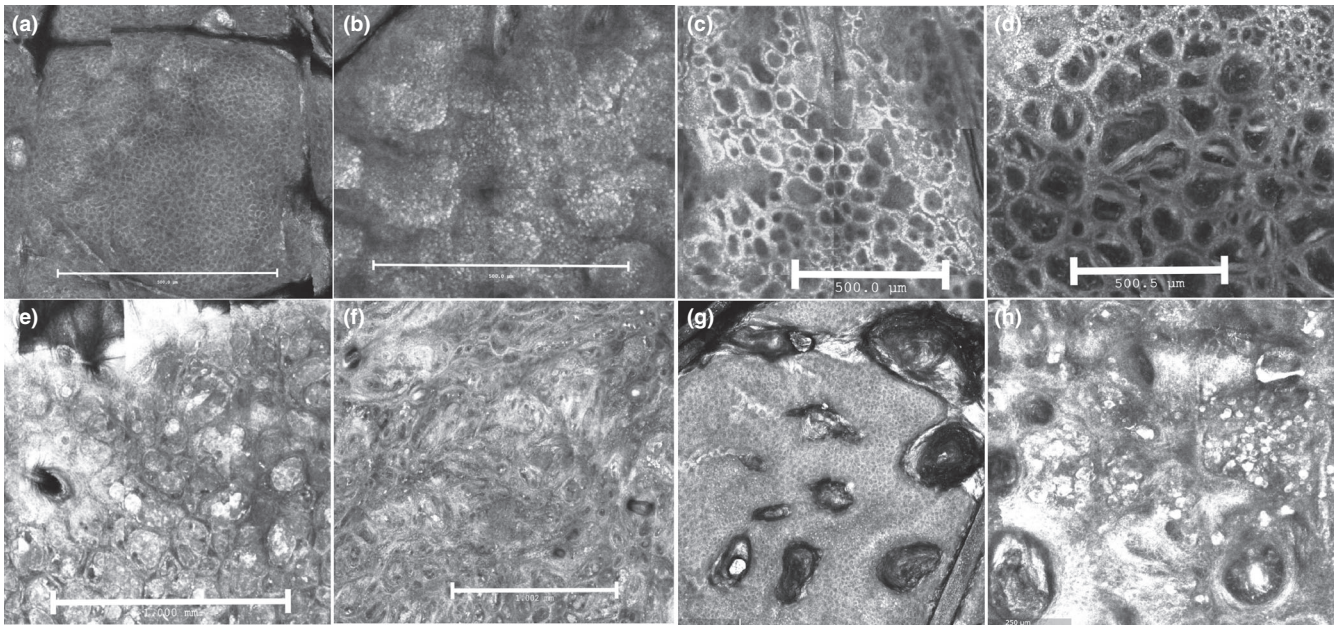

Figure 7 Reflectance confocal microscopic features of CMN. (a) RCM images of a small-sized CMN at the spinous-granular layer of the epidermis. Epidermis shows a typical honeycomb pattern with dermatoglyphics. (b) RCM mosaic at the level of supra-papillary layer showing basal keratinocytes pigmentation with hyper refractile bright dots. (c) RCM image of a small-sized CMN at the level of dermo-epidermal junction showing a ringed pattern, which is a dark papilla outlined with bright pigmented epidermal basaloid cells. (d) RCM image of a small-sized CMN at the level of dermo-epidermal junction showing a mesh work pattern. Meshwork pattern is a distinctive mesh characterised by small dark holes surrounded by clearly thickened interpapillary spaces. Dermal papillae usually appear smaller than ringed pattern and are not outlined by rings. (e) RCM image of a medium-sized CMN at the level of dermo-epidermal junction showing clod pattern. Clod pattern shows numerous densely packed, well-demarcated refractile clusters of melanocytes, usually within dermal papillae. (f) RCM image of a medium-sized CMN at the level of dermo-epidermal junction showing a multicomponent pattern which consists of clod and meshwork pattern. (g) RCM image of a small-sized CMN at the level of the granular layer showing corneal cysts, which are large, highly refractile intra-epidermal structures that correlated with milia-like cysts in dermatoscopy. (h) RCM image of a small-sized CMN at the level of dermo-epidermal junction and dermis showing clusters of white bright structures in the papillary dermis with surrounding epidermal lentiginous hyperplasia.

structures that correlated with milia-like cysts in dermatoscopy) (Fig. 7g) at the dermo-epidermal junction,

-Clusters of white bright structures in the papillary dermis (Fig. 7h), a previous case series by *Marghoob et al.* showed the value of RCM in both diagnosing CMN and diagnosing melanoma arising on CMN. RCM showed pagetoid spread of the melanocytes with a chaotic growth pattern as well as atypical single cells within the nests and dendritic processes of the large melanoma cells in this report.[79] Dermatoscopic and RCM images of melanoma arising on CMN are given in Figure 8a-e.

Transient erosion is another finding that can be seen in infants due to skin fragility in the neonatal period from trauma during delivery, but these erosions tend to heal spontaneously over days to weeks, and these lesions are mostly non-malignant. However, if there is persistent ulceration or change in CMN, a biopsy is required to confirm the diagnosis and exclude melanoma.

TREATMENT OPTIONS IN CONGENITAL MELANOCYTIC NAEVI

Targeted therapy for symptomatic large/giant CMN has been reported in the literature in some cases. In one case with BRAF fusion treated with MEK inhibitor, nodular lesions showed flattening associated with a subsidence of symptoms.[49]

The recommendation for excision of CMN is controversial. Surgical excision for large/giant CMN is often attempted in the first few years of life because at that stage the skin tends to be more pliable and elastic. The surgical approach depends on the size and location of the CMN. Tissue expansion flaps/grafts, or staged excisions are usually performed, and multiple operations may be required. The temporary use of tissue expanders to reduce the number of operations may be employed. Self-filling tissue expanders and other types of needle-free expanders can avoid the repeated painful filling.[80] However, there are certain drawbacks associated with the surgical approach, such as short-term discomfort with limitation of physical activity, risk of wound infection, risk of anaesthetic complications, risk of poor wound healing, restriction of mobility due to scarring, pain and pruritus as well as psychological impairment due to lifelong scars.[15] An example of long-term result of surgical excision of a medium-sized CMN given in Figure 9.

Recent work published by *Kinsler et al.* showed that final CMN colour is determined genetically, being related to

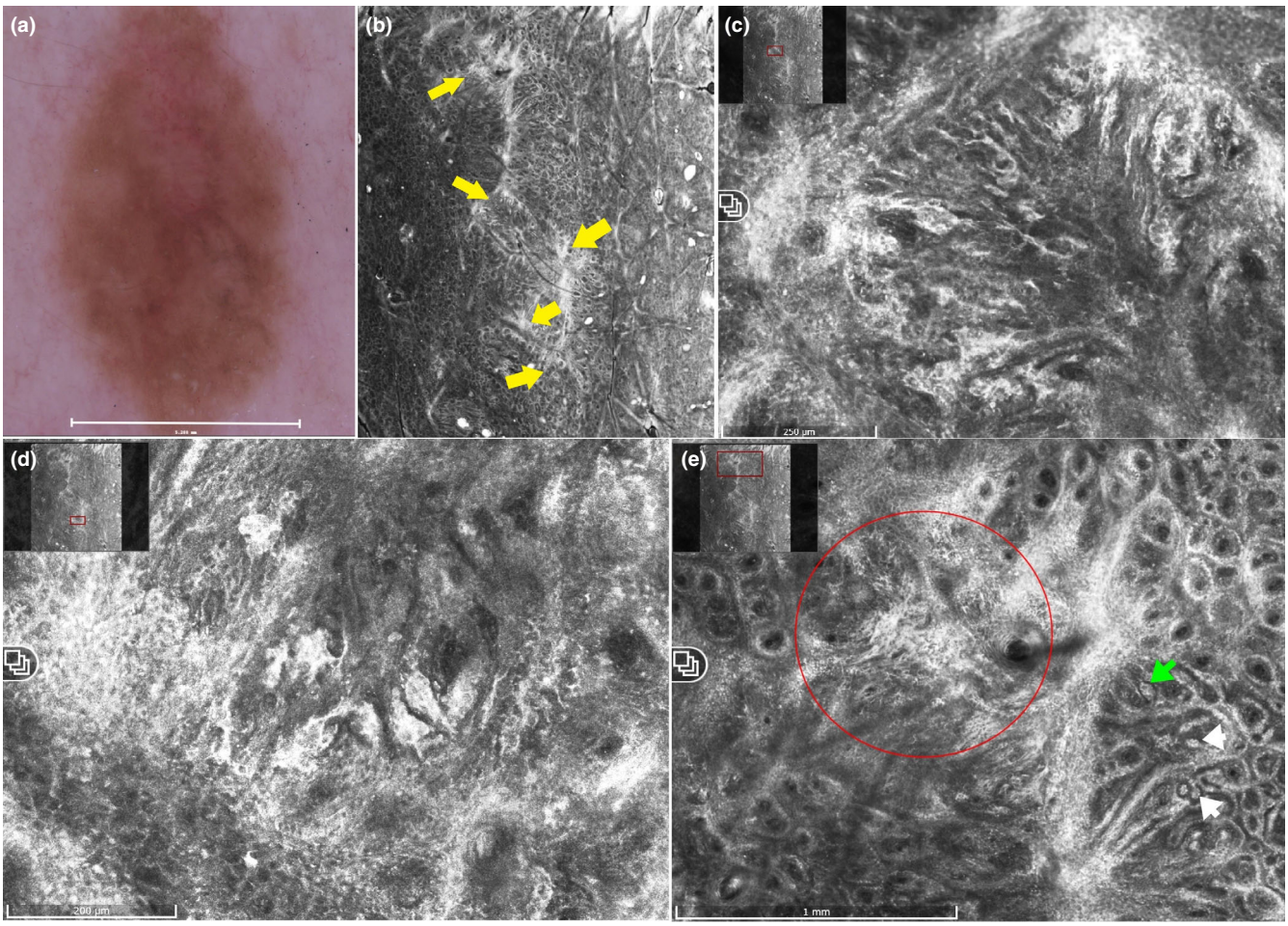

Figure 8 Dermatoscopic and RCM images of a melanoma arising on a small-sized CMN. (a) Dermatoscopy shows a 10 x 6 mm diameter pigmented lesion with colour variegation, greyish pigmentation at 3 o'clock, and polymorphous vascular pattern on the upper middle part of the lesion. (b) RCM mosaic at the level of dermo-epidermal junction shows a disarranged pattern adjacent to a regular ringed pattern (yellow arrows). (c) Higher magnification of the middle part of the lesion shows atypical dendritic cells and atypical melanocytic nests. (d) Higher magnification of the lower part of the lesion shows polygonal, hyperreflective, single, nucleated melanocytes with non-edged papillae. (e) RCM mosaic of the upper part of the lesion at the dermo-epidermal junction. There is a disorganised area (red circle) adjacent to a benign naevus component which consists of junctional (white arrows) and dermal melanocytic nests (green arrow).

normal skin colour and inherited pigmentary phenotype. In addition, the final colour of the lesion is independent of the colour of CMN seen during the first 3 months of life. The authors concluded that surgical intervention with incomplete removal does not alter the final colour of CMN as they noticed the same pigmentation pattern in both treated and untreated parts of CMN.[8]

Several small studies have reported improvements and high levels of patient's satisfaction after superficial removal techniques (dermabrasion, laser, curettage); however, improvement in colour in these studies was judged immediately after intervention, regardless of the fact that re-pigmentation usually occurs after years of surgery.[81,82]

Dermabrasion is a method involves the removal of the superficial epidermis using a high-speed diamond burr.[83] German CMN registry showed that 42.5% of surgically treated patients had undergone dermabrasion.[84] Dermabrasion showed initial aesthetically good results in some studies.[85] However, in long term, there is frequently no significant aesthetic improvement as the lesions commonly show re-pigmentation[86] and scarring is a disfiguring complication.[87] Thus, dermabrasion for CMN should be reviewed critically and they are not accepted as a part of modern CMN treatment.[87]

Laser treatment (with ablative and pigment-specific lasers) is another therapeutic option for CMN where surgical removal is not feasible or to avoid surgery. However, there is a caveat with this modality, since lasers do not penetrate to the deep dermal structures and therefore melanocytes located in the dermis remain after treatment. Re-pigmentation rate years after laser treatment varied between 10-82% different studies.[88-90] Due to frequent re-pigmentation later in life, laser based procedures are primarily used for cosmetically sensitive areas such as nasal

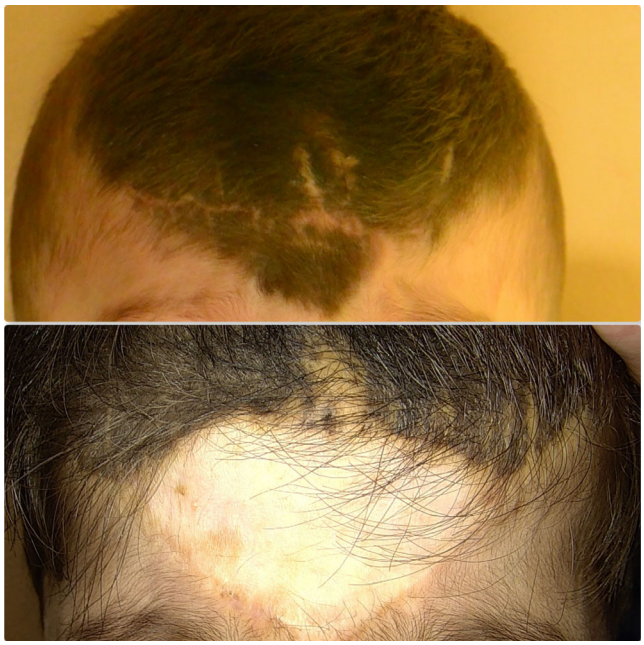

Figure 9 A medium-sized CMN located on the frontal scalp of a 3-year-old male. Staged excision of the lesion has been performed by the plastic surgery department. After 3 stages at the age of 7, a hypopigmented, sharply demarcated disfiguring scar is visible on the forehead of the patients.

tips, periorbital areas, glabella, and cheeks and combined with other plastic surgery procedures.[87]

CONCLUSION

CMN are a heterogenous group of melanocytic neoplasms, presenting with varied clinical features and associated comorbid conditions. Efforts to produce a new system to classify CMN continue since the old classification failed to include many variables defining these heterogenous lesions. While small CMN carry a negligible risk of progression to melanoma and associated CNS abnormalities, large/giant CMN requires meticulous attention. Large/-giant CMN is associated with an increased rate of CNS involvement, thus these patients should be managed with a multidisciplinary approach. Identifying mutations in CMN patients may, in the future, facilitate treatment of the potential complications arising from these lesions by employing targeted yet therapies. Dermatoscopic, and clinical follow-up of CMN is required to detect melanomas in early stages, especially in large/giant CMN. RCM can be helpful in both diagnosing CMN and melanoma arising on CMN in occasions. Radiologic evaluation is recommended for high-risk patients and patients with neurologic symptoms. The benefits of surgical intervention in early childhood and laser ablation are debatable with the current data and dermabrasion is not accepted as a treatment option. Treatment modalities introduced in the literature do not decrease the risk of melanoma development and it can cause disfiguring scars, potentially affecting the psychosocial lives of the affected individuals.

QUESTIONS

1 Which of the following statement is not true for congenital melanocytic naevi (CMN)?

- A CMN are hamartomas of the skin which originate from neuroectoderm.
- B CMN are usually present at birth.
- C CMN is inherited in an autosomal recessive pattern.
- D Melanomas can occur as a complication of CMN.
- E CMN may occur due to the mutations of NRAS/BRAF genes.

2 Which of the following statement is false about melanomas arising from congenital melanocytic naevi?

- A The risk of melanoma development in small/medium size CMN is equal to normal population.
- B Melanomas in small/medium-sized CMN tends to occur at the periphery of the lesion.
- C Melanoma risk on large/giant sized CMN is 5-15%.
- D Removal of CMN reduces the risk of melanoma development.
- E 1/3 of melanomas develop primarily in CNS in individuals with large/giant CMN lesions.

3 Which of the following statement is false about neurocutaneous melanocytosis (NCM)?

- A NCM is associated with diffuse or localized proliferations in brain parenchyma or meninges.
- B It may be symptomatic due to mass effect in central nervous system (CNS).
- C Most of the patients with CMN shows no symptoms
- D Symptomatic CNS involvement is associated with high risk of CNS melanoma development.
- E NCM symptoms always present in the first 2 years of life.

4 What is the most common post-zygotic mutation causing CMN?

- A NRAS
- B BRAF
- C GNAQ/GNA11
- D H-RAS
- E PTEN

5 MEK inhibitors have been reported to improve the symptoms in patients with large/giant CMN.

- A True
- B False

6 Which of the following statement is not true regarding CMN treatment?

- A Surgery is recommended in the first few years of life
- B Re-pigmentation of the surgically treated area is often seen as the child ages

C Final CMN colour is genetically determined, and studies have shown the same pigmentation patterns in both surgically treated and untreated area.
D Final colour of CMN is dependent of the colour seen in the first three months.
E Targeted therapies might be a therapeutic option for CMN in the future.

7 Which dermatoscopic patterns can be seen in CMN?

A Reticular pattern
B Cobble stone appearance
C Atypical dots and globules
D Perifollicular pigmentary changes
E All of the above

8 BRAF mutant CMN tends to be more nodular and less hairy compared to NRAS mutant CMN.

A True
B False

9 New classification schema proposed for CMN includes the parameters below except:

A Rugosity
B CNS involvement
C Size
D Colour
E Location

10 Differentiating proliferative nodules arising on CMN from melanoma is possible with genetic testing.

A True
B False

1-C, 2-D, 3-E, 4-A, 5-A, 6-D, 7-E, 8-A, 9-B, 10-A.

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