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Melanoma on congenital melanocytic nevi

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ABSTRACT

Among nevus-associated melanomas, which overall account for 20%-30% of all melanomas, those arising specifically in congenital melanocytic nevi are infrequent, but can be disproportionately frequent in childhood and adolescence. Congenital melanocytic nevi (CMNi) are common benign melanocytic tumors that are present at birth or become apparent in early childhood. They are classified based on the projected adult size. Small and medium-sized CMNi are frequent, whereas large/giant CMNi (over 20 cm in diameter) are rare, but can be associated with high morbidity due to marked aesthetic impairment and the risk of neurocutaneous syndrome or melanoma development. In this setting, melanomas can appear in early childhood and are very aggressive, while the risk of small-medium CMNi of developing melanoma is low and similar to non-congenital melanocytic nevi. Histologically, most melanomas on CMNi initiate their growth at the epidermal-dermal junction, but in large/giant CMNi they can develop entirely in the dermis, in deeper tissues, or in extracutaneous sites (especially in the central nervous system). Most CMNi harbour an *NRAS* mutation, but other genes are rarely involved, and gene translocations have recently been described. However, no prognostic implications have been associated with the CMN genotype. Melanomas developed on CMNi harbour additional molecular alterations to which the aggressive clinical course of these tumors has been attributed. This review covers the distinctive clinical and pathological aspects of melanomas on CMNi, and includes the epidemiology, etiopathogenesis, clinical and dermoscopic presentation, histological and molecular characteristics, as well as tumour behaviour.

1. Introduction

Nevus-associated melanoma represents a small minority of all cutaneous melanomas estimated at around 20%-30% depending on population and age. However, it remains a topic of debate [1,2]. Different hypotheses have been put forward regarding a possible distinctive biological origin and behaviour as well as risk factors other than *de novo* melanoma.

Melanomas that arise in a pre-existing nevus especifically of the congenital type also represent a small proportion of cases. However, the high prevalence of congenital melanocytic nevi (CMNi) in children and young adults, and the higher proportion of melanoma in congenital nevi in these patients make this field of great interest. Epidemiologically, clinically, dermoscopically and histopathologically, melanomas associated with CMNi can present with some distinctive characteristics, especially those cases that arise in large and giant CMNi.

2. Congenital melanocytic nevi

2.1. Definitions and epidemiology

Congenital melanocytic nevi (CMNi) are benign, pigmented

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melanocytic tumours which are present at birth or develop within the first weeks of life. Melanocytic nevi that appear within the first years of life are also considered CMNi (tardive CMNi) since clinically and pathologically they are indistinguishable[3].

According to the expected size at adulthood (PAS, from projected adult size), CMNi are classified into three main categories: small (less than 1.5 cm), medium (1.5–20 cm), and giant when they are expected to be larger than 20 cm (Fig. 1).

Solitary, small and medium CMNi are frequent, with an incidence of 1%-6% in newborns, and do not seem to imply different risks from any other acquired melanocytic nevus, and they do not present syndromic associations. Indeed, most nevus-associated melanomas appear on common acquired nevi more than CMNi. The considered giant CMN include large (PAS=21–40 cm) and giant (PAS >41 cm) nevi, is a minority condition (1 in every 20,000–500,000 newborns), and cover a spectrum of genetic syndromes with highly variable phenotypic expression (Orphanet code ORPHA-626). They can affect almost the entire body surface and have been associated with a complex syndrome of variable expressivity[3–5]. The presence of multiple medium-sized CMNi is included in this same spectrum of the large/giant nevus, given the possibility of syndromic association [6,7]. Giant CMN present recurrent anatomical distribution patterns (so called 6B patterns)[8] and the recently described 7B bonce (on the head)[9] or biker gloves [10], supporting the classification according to their embryologic

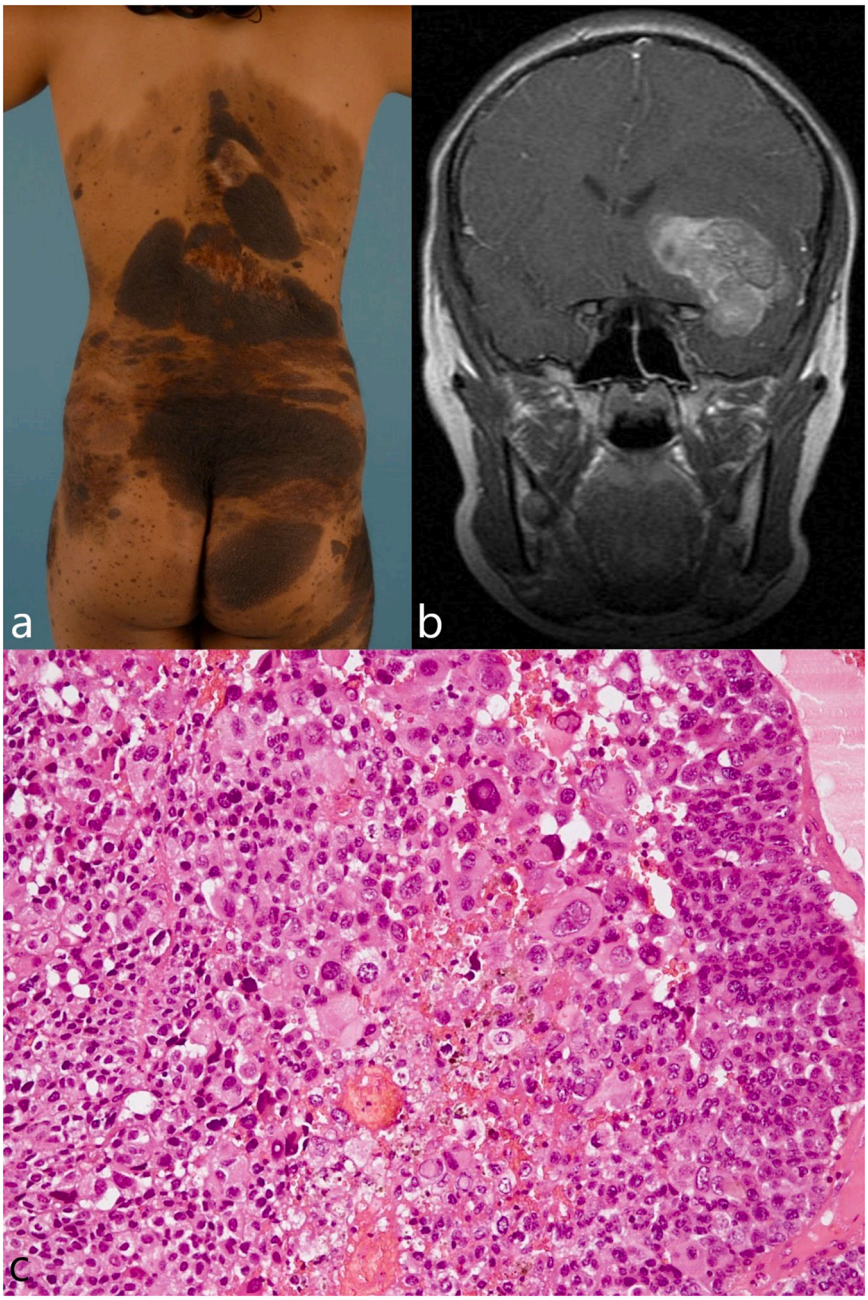

Fig. 1. Primary CNS melanoma associated with giant congenital melanocytic nevus (CMN). Giant CMN classified as spilus-like and bathing B3 type, covering the majority of the back, buttocks and genital area (a). She had presented normal psychomotor development with normal transfontanellar ultrasonography at birth. At the age of 10 she presented with diplopia and vomiting, and physical examination found palsy of the sixth right cranial nerve, and cranial magnetic resonance imaging demonstrated a left frontotemporal intraparenchymal tumor, 4 cm in diameter, with mass effect and edema, that compressed the left lateral ventricle, shifting the midline to the right (b). The tumour in the CNS was removed. The histopathological study showed a proliferation of highly atypical melanocytic cells, with necrosis foci (Hex100) (c).

nevogenesis. Beyond size and location, giant CMNi present enormous variability in their appearance and potential life-long complications. There have been different attempts to classify them depending on the color heterogeneity, surface rugosity, hypertrichosis, nodularity, and numbers of "satellites". "Satellites" means disseminated, multiple small CMN that appear from birth through the first years of life (Krengel's quantitative classification C, R, H, N, S) [3].

2.2. Peculiarities and relevance of giant CMNi

The importance of large/giant CMNi lies in the fact that these lesions may occur as isolated endophenotypes or as part of a "CMN syndrome" with highly variable phenotypic expression [6]. Patients with large/-giant CMNi have a highly increased risk of developing pediatric or adult melanoma within the lesion and as great a risk of a non-cutaneous melanoma within the viscera or, particularly, the central nervous system (CNS) - often associated with leptomeningeal melanocytosis[11, 12]. The lifetime risk of melanoma seems proportional to lesion size, reaching up to a 15% risk for lesions >40 cm [13], but is estimated to be on average about 5%.

More frequently, about 25% patients may present leptomeningeal melanocytosis or other CNS abnormalities, with or without symptoms. The spectrum includes brain tumors [14], Dandy-Walker malformation [15], arachnoid cysts tethered spinal cord, hydrocephalus or epilepsy [16,17]. The presence of CNS abnormalities in early MRI is considered the most predictive risk marker to develop melanoma[18,19]

Patients may suffer severe psychological consequences as a result of the visibility of their condition, including social problems and behavioral disorders. These issues can arise because of impaired self-image [20], and the discomfort caused by multiple invasive treatments and even by the unsightly appearance of surgical scars [21].

Summary of potential complications of patients with large/giant CMN: - Syndromic association consisting of melanocytic deposits in the central nervous system (CNS), with or without other developmental associations (Giant CMN syndrome), in 10–25% of patients. - Risk of developing melanoma in childhood or during adult life, whether cutaneous, soft tissue, lymph node or CNS (5%-15%). - Development of benign or malignant tumors, such as plexiform neurofibromas, melanocytomas (proliferative dermal nodules) or soft tissue sarcomas (2%-10%). - Highly variable affectation of body image throughout life, with unpredictable evolution/involution of the nevus and its possible associated deformities (100%).

2.3. Histopathology and genetics of the congenital melanocytic nevi

2.3.1. Histological features

The diagnosis of CMN is clinical, the essential feature being its presence at or immediately after birth. Histologically, as with acquired melanocytic nevi, they can be junctional (especially small CMN), or, more frequently, compound or intradermal. The melanocytic cell proliferation of a CMN begins at the dermal-epidermal junction, and later tends to extend to the dermis. Although histological features are usually not exclusive to CMN, some are characteristic and suggestive of a CMN diagnosis [22] [23,24]:

- Large size and depth of the lesion. A melanocytic nevus over 1.6 cm diameter is suspected to be a CMN [23]. Depth of the nevus cells correlates with the size of the CMN [25]. Frequently, CMNi reach deep parts of the dermis and subcutaneous tissue. In giant CMNi, nevi cells can involve deep fascia and muscular tissues.

- Periadnexal, perivascular and perineural spread. Typically, CMNi reach deep tissues following adnexal structures (follicles and eccrine ducts and glands). Occasionally, nevus cells can infiltrate hair arrector muscles, the sebaceous gland or epithelia of eccrine glands. Nevus cells can also migrate along vessels and nerves [26].

- Architecture of the melanocytic proliferation. Typically CMNi display in a band-like architecture occupying the entire dermis span. In addition, Indian-file or reticular pattern in which nevus cells can be seen between normal collagen fibers can be seen.

- Extensive neural differentiation. This feature usually occurs at depth but sometimes is very extensive and CMNi can resemble dermal neurofibromas, especially on the scalp. In addition, other cell type differentiation has been described in some giant CMNi, such as osseous, chondroid or muscular or even undifferentiated embryonic tissue.

- Hamartomatous features. Hamartomatous features such as elastic tissue nevus can be seen beside the nevus cells of CMNi. The presence of an increased number of terminal hairs raises the suspicion of CMN.

- Atypical features. Elongation of the rete ridges of the epidermis, presence of dysplastic-like changes in the junction, presence of balloon cells, even focal pagetoid spread can be seen in CMNi, without evidence of melanoma progression [27]. In the newborn, CMNi can show highly atypical features, such as a high mitotic index and pagetoid spread without unfavourable follow-up.

2.3.2. Special CMN subtypes

Nevus spilus is clinically characterized by a café-au-lait macule with superimposed more-intensely pigmented macules and/or papules and can be acquired or congenital.

In the latter condition there is an extensive hyperpigmentation of the epidermal basal layer along with slight junctional melanocytic lentiginous proliferation, and the frequent presence of dermal melanocytic component, showing the clinical picture and histology of a CMN [28].

Other nevus and melanocytomas subtypes that can develop as congenital forms include Spitz nevus, blue nevus, and pigmented epithelioid melanocytoma. Congenital blue nevi especially affect the scalp and face [29]. These lesions tend to be large and deep following adnexal and neural structures. The proliferation can be large enough to produce dystocia. Pigmented epithelioid melanocytomas are composed of a proliferation of large and deep epithelioid, heavily pigmented melanocytes [30].

2.3.3. Pathogenesis & genetics

CMNi usually develop from a somatic postzygotic mosaicism for *NRAS*. Genetic events occur in melanoblasts or their immediate progenitor cells, during embryogenesis. A multipotential stem cell from the neural crest can bear the somatic mutation. After colonizing the epidermis, melanoblasts transform into melanocytes. Due to the early nature of this development alteration, nevus cells bearing the same genetic alteration can affect the total thickness of dermal and hypodermal tissues and can be found in leptomeninges, a phenomenon called neurocutaneous melanocytosis [31]. Activating missense mutations of codon 61 of *NRAS* (predominantly *NRAS* Q61K/L/R) are the most frequent genetic alterations associated with CMNi, especially in large and giant CMNi [32–34]. Affected CNS tissues share the same mutation profile as the cutaneous lesions of the same patient [32]. In small and medium-sized CMN, *BRAF*V600E mutations predominate [35]. Nevertheless, in a minority of giant CMN, even those showing neurocutaneous syndrome, *BRAF*V600E has been detected and has been related to the presence of multiple clinically evident dermal and subcutaneous nodules composed of mature adipose tissue [35]. Single cases of fusion transcripts have also been described, such as *ZEB2::ALK*, *SOX5::RAF1*, and *SAAS6::RAF1*, and *AKAP9::BRAF* in *NRAS* wild type giant CMNs [34,36, 37].

In nevus spilus-type CMN, genetic studies have also shown *NRAS* mutations, including Q61H, G13R, and Q61L subtypes [34,38,39].

More infrequently, mutations involving other genes, such as *PIK3CA, KRAS, GNAQ, APC, MET, EGFR,* and *MAP2K1* have been described in giant conventional and spilus-type CMNi [34].

Nevertheless, the molecular profile of the CMN does not have prognostic implications [35].

3. Melanoma on congenital nevus

3.1. 3.1. Epidemiology

As mentioned above, the lifetime incidence of melanoma is higher in large/giant and multiple CMN than in medium sized or small CMN. It widely ranges from 5% to 15%, with an average risk of 8.2% [22,27,40–42]. In a European cancer registry study, patients with a giant CMN had a 51.6-fold higher risk of developing a melanoma when compared to the general population [43]. The great variability reported in the incidence of melanoma in CMN depends mainly on the type of study. In retrospective studies, it reaches 15% of cases, while prospective studies from academic referral centers show significantly lower average rates, ranging between 2% and 5%, in a follow-up period of 4.5–7.3 years [22]. The highest risk of melanoma development occurs in childhood, usually before age 10, and this risk progressively decreases with age [22,41]. In fact, in children $\leq$ 10 years old, melanomas developed in a CMN represents around half of all cutaneous melanomas [44]. After this age the incidence decreases and it is similar to that of melanomas on CMN in adulthood, representing about 31.6% of all melanomas [44].

There is controversy about the incidence of malignant transformation in small or medium–sized CMNi. Some authors believe that there is no risk for melanoma development, whereas in other studies this incidence reaches the rate of 2.6% [22].

3.2. Clinical and dermoscopic characteristics

3.2.1. Melanoma arising in small and medium size CMN

There are few studies specifically focused on the clinical presentation of melanoma arising in CMNi, the majority of the evidence comes from the field of nevus-associated melanomas. Nevus-associated melanomas tend to occur in younger patients than *de novo* melanomas (mean age 49.1 years (SD16.76)) [45]. There is no sex predominance. Most cases present on the trunk and meet the clinical ABCD-E rule; Asymmetry, irregular Borders, multiple Colors, Diameter greater than 6 mm and Evolution-enlargement. Any congenital nevus that presents with a nodule, asymmetric enlargement or relevant changes in adulthood should be evaluated to rule out melanoma (Figs. 2 and 3).

The clinical challenge lies in two issues: 1. the classical ABCD-E rule is not enough to identify early melanomas arising in congenital nevus, and 2. the main population at risk of developing melanoma in a congenital nevus are young adults, and melanocytic nevi will change and grow during the first decades of life.

Consequently, dermoscopy, an in vivo non-invasive imaging techniques used in daily routine by dermatologists, is mandatory. Dermoscopic evaluation shows frequent features associated with melanoma, including the presence of multiple colours and asymmetry of structures or architectural disorder. The most robust and specific local features of malignancy include atypical network, irregular globules and dots, negative network, blue white veil, pseudopods/streaks, regression (blue-grey dots and white structures), atypical vessels (other than comma vessels typically seen in the dermal component of nevus), and

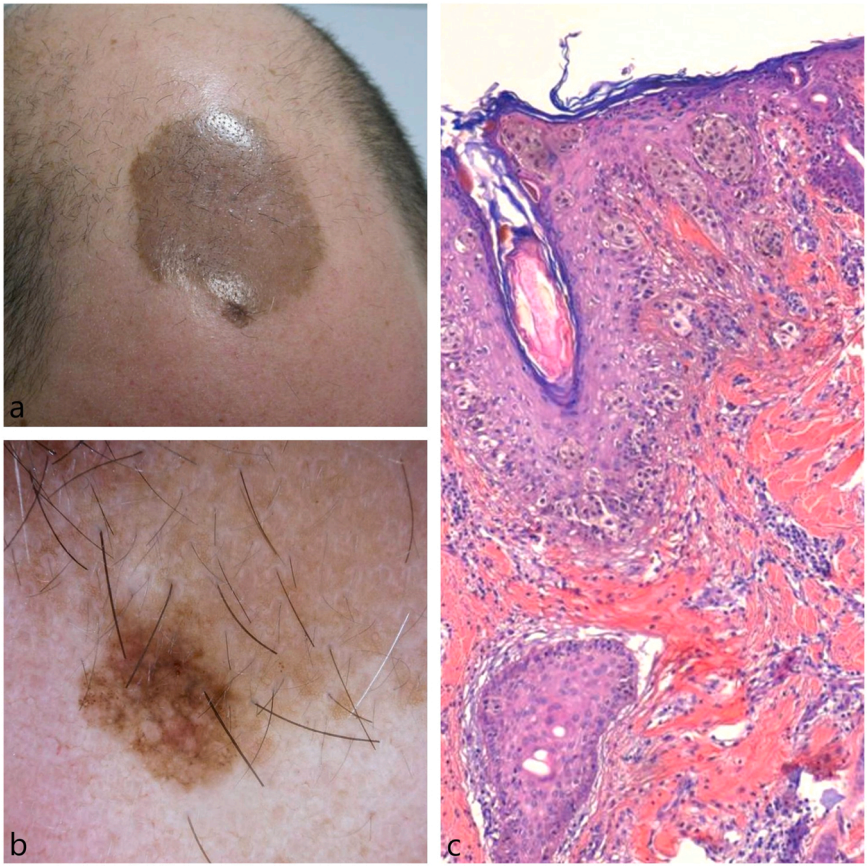

Fig. 2. In situ melanoma associated with medium-size CMN. Clinical appearance shows a light brown macule, 10 cm in diameter, on the scalp of a patient in his forties. Focal and asymmetric hyperpigmentation appeared (a). Dermatoscopy features of the light brown macule demonstrated homogeneous fine reticulated pigmentation, while the focal hyperpigmented area showed irregular globules in an angulated conformation around follicular openings, raising suspicion of melanoma (b). The lesion was excised. Histologically, the atypical macule was composed of atypical melanocytic nests that grew along the epidermal-dermal junction with pagetoid spread, showing the histological characteristics of an in situ superficial spreading melanoma. The melanocytic cells were pigmented and had atypical nuclei (HEx100) (c).

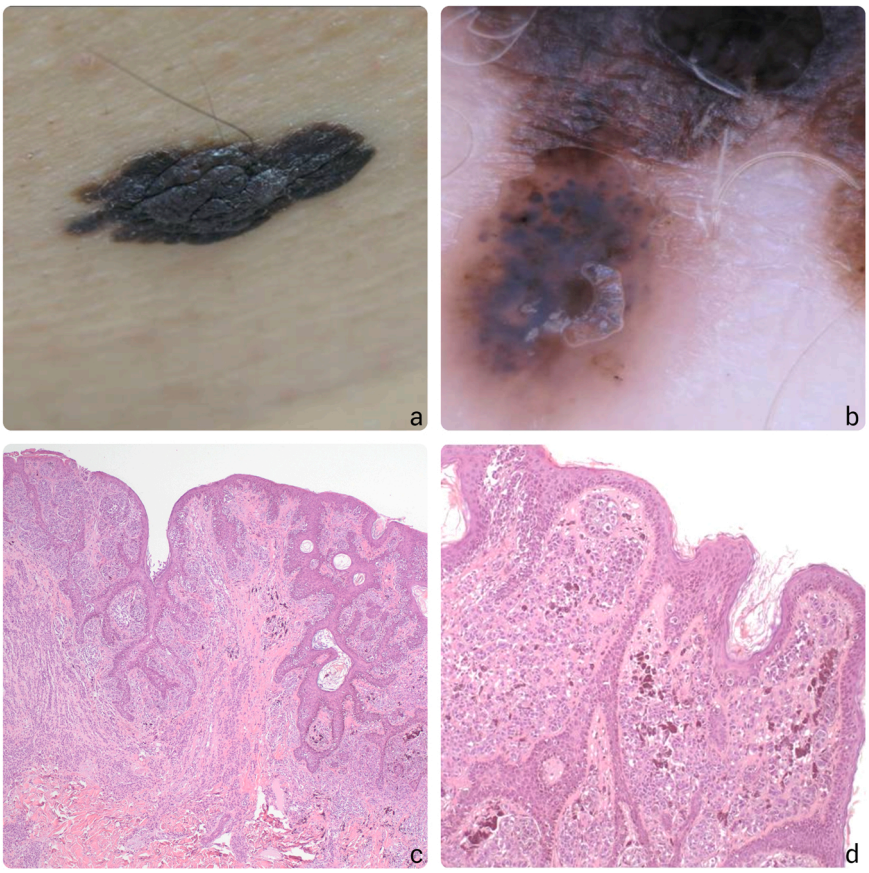

Fig. 3. Invasive melanoma associated with small-size CMN: Dark brown and black papillomatous CMN with terminal hair that presented enlargement and changes at the periphery in a patient in his thirties (a). Dermoscopy showed atypical irregular globules at the periphery, while the remaining tumour presented blue-black homogeneous pigmentation over a reticular background (b). The lesion was removed and histologically two distinct components were seen. On the left of the picture, a CMN component is seen, composed of small, homogeneous cells that occupy the dermis and spread in depth following adnexal structures. Overlying the CMN component, and especially on the right of the image, an invasive melanoma is identified (HEx40) (c). The melanoma component was composed of atypical pigmented cells, which infiltrate the dermis, along with scattered melanophages (HEx100) (d).

shiny white structures [46,47] (Figs. 2 and 3). In a retrospective study that compared CMNi to melanomas arising in CMNi, the most predictive dermoscopic features related to melanoma on small CMN were atypical or negative network, shiny white lines and gray angulated lines [48].

3.2.2. *Melanoma associated with large and giant CMN*

In addition to cutaneous melanomas, which would be similar to those developed in small type CMN, patients with large and giant CMNi can develop lymph node or subcutaneous primary melanoma, as well as CNS primary melanoma. These rare complications can present with the symptomatic disease depending on the primary location of the tumor or metastatic disease. [2]

3.3. *Histopathology and genetics*

In the small and medium size CMNi, and in most large and giant CMNi, melanomas usually initiate their growth at the dermal- epidermal junction. They can frequently share the morphological characteristics of a superficial spreading melanoma, showing the development of irregular tumoral nests in the junction with a tendency to pagetoid growth (Figs. 2 and 3). Sometimes, melanoma cells display in a lentiginous pattern. They may progress from an *in situ* stage to a superficial invasive radial growth phase and a subsequent deeper vertical growth phase (Figs. 2 and 3). However, melanomas on giant CMNi can develop entirely in the dermis, hypodermis, or even in deeper tissues [49]. This situation has been especially reported in giant CMN in prepubertal patients [22,27].

Melanoma cells can be epithelioid, microcytic, or spindle shaped [22]. They usually show a poor demarcation with nevus cells in continuity, but sometimes are well demarcated and have an expansile architecture. Histology may show high-grade atypia, high mitotic index (above 2/mm^2), necrosis and ulceration. One case of melanoma with rhabdomyosarcoma differentiation developed from a CMN has been reported [36]. Nevertheless, the development of a sarcoma (non-melanocytic) from a giant CMN, showing the features of a malignant schwannoma, rhabdomyosarcoma or liposarcoma, has also been reported [50,51].

As mentioned above, melanomas can also develop at extracutaneous sites in patients with giant CMNi. In patients with neurocutaneous syndrome, melanomas may appear in the CNS (Fig. 1), as well as in the lymph nodes [27].

The development of a malignant blue nevus on a congenital blue nevus has been reported [50,52].

The molecular progression underlying the malignant transformation of a CMN has demonstrated the addition of molecular events that take place in melanoma development, in agreement with a multistep model of melanoma progression. Loss of *NRAS* heterozygosity, amplification of mutated *NRAS*, and additional loss of *CDKN2A* have been reported as a genetic progression of melanoma developed from a preexisting *NRAS*-mutated CMN [32,53]. Other genetic alterations detected in the melanoma progression involve *TP53, KIT, KDR, MC1R*, *MAP2K1* and *MITF* genes, in addition to *TERT* activation through promoter hypermethylation, that could contribute to the aggressive clinical behavior of these melanomas [53–55].

Multiple gains and losses through comparative genomic

hybridization (CGH) techniques have been described in melanomas on CMN [32,54,56], as occur in other melanoma types, and can be useful for diagnostic purposes in difficult cases.

3.4. Differential diagnoses. Benign and intermediate proliferations in CMN

3.4.1. Proliferative nodules

To recognize benign or intermediate proliferations and conditions and to differentiate them from malignant melanoma on CMN can be challenging. The most important entity in this setting is the proliferative nodule (PN). PNs can be present at birth, but can also develop during childhood. They usually grow for several weeks and then stabilize [42]. PNs usually measure 0.5 cm to 2 cm, but cases up to 5 cm. have been reported. They may have a soft or firm consistency. Although they can be pigmented, they are frequently pink and less pigmented than the surrounding CMN. PNs are often multiple, especially in giant CMN. They usually arise in the dermis of the CMN, but junctional activity, lentiginous growth, and pagetoid spread have been described in PNs [49,56]. PNs can be well demarcated and may show an expansile growth (Fig. 4), or conversely PN cells can blend with the surrounding CMN [57]. The term 'cellular nodules' has been proposed to describe nodules showing a greater cellularity but without mitosis or proliferative signs [57]. Several histological patterns can be seen: they can be composed of epithelioid, microcytic, or spindle-shaped cells (Fig. 4), as occur in melanomas on CMN. However, tumour cells lack high-grade atypia, and mitoses are absent or scarce[27,58] (Fig. 4). Nevertheless, proliferative features can be seen, and up to 2 mitoses/mm^2 can be counted, whereas in melanomas the mitotic count is usually higher [49,57]. Other histological features that favour the diagnosis of melanoma are high-grade atypia, necrosis, and ulceration [49,56]. Because of the histological overlapping of PN with melanoma in some cases, ancillary techniques are required. The immunohistochemical pattern of positivity of HMB45 and p16 do not discriminate PN from melanoma arising in CMN [59]. Recently, novel immunohistochemical markers have been introduced for the assessment of PN. Since different DNA metylation patterns have been observed in PNs in comparison with melanomas, the immunohistochemical expression of H3K27me3 has been proven useful to differentiate both entities [60]. HK27me3 nuclear expression is usually preserved in PN, whereas melanomas frequently lose this expression [60,61]. Recently, the nuclear expression of preferentially melanocytic antigen (PRAME) has been investigated in melanomas. One study has shown PRAME expression in two melanomas developed on CMN tested, whereas 21 but two PNs were negative for PRAME in $\geq$ 75% of tumoural cells [62].

The study of copy number variation (CNV) using cytogenetic techniques, such as comparative genomic hybridization (CGH), has proven useful to differentiate both entities. CMNi and cellular nodules with no atypia or proliferative signs may not show CNV abnormalities [56]. PNs showing a mild or moderate atypia and proliferative signs, may show alterations involving entire chromosomes [49,56,63]. For this reason, FISH melanoma multiprobe can give positive results in PNs and can be erroneously interpreted as melanomas [59].

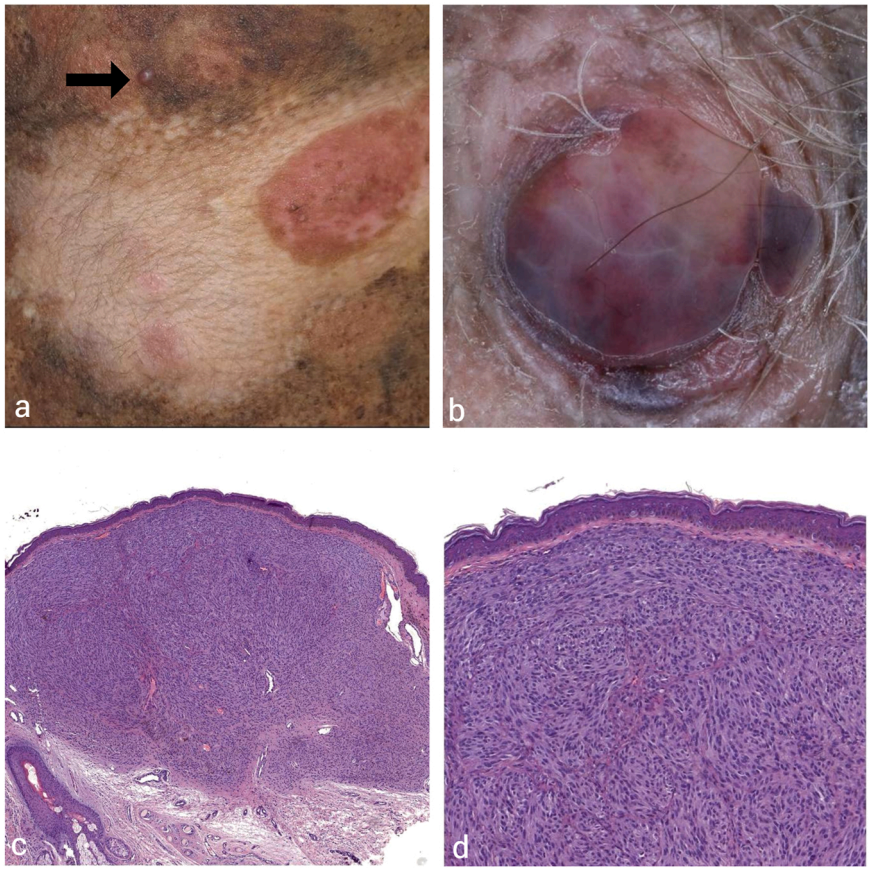

Fig. 4. Proliferative nodule developed in a giant CMN: (a) 9 year-old girl affected by giant CMN, spilus-like and body B6 type, affecting most of the trunk and associated with hundreds of satellites. Complex phenotype of the giant CMN also includes multiple colours over the pigmented background, hypertrichosis and nodularity. A new firm and reddish nodule was detected on the trunk (arrow). (b) Dermoscopy image showed pink and bluish unspecific pigmentation. The nodule was excised. Histologically it was composed of a well demarcated nodule with expansile growth in the dermis, without epidermal ulceration (HEx40) (c). The nodule was composed of spindle cells with mild or moderate atypia, and low mitotic count (HEx100) (d).

3.4.2. Combined CMN with deep penetrating tumours (WNT-activated melanocytoma)

Deep penetrating tumours (recently called WNT-activated melanocytomas) can arise from a pre-existing CMN, leading to differential diagnoses difficulties clinically and histopathologically [64]. The WNT-activated melanocytoma component can show high-grade atypical histological features and requires the histopathological and molecular study of tumours to establish an accurate diagnosis [65].

3.4.3. Spitz nevus

Solitary or agminated Spitz nevus development arising in spilus-type nevi has been reported. Recently, an agminated Spitz nevus arising on a pre-existing congenital hyperpigmented macule showing a three-way complex rearrangement of TRPM1-PUM1-LCK has been reported [66].

3.5. Treatment & clinical follow-up

Cutaneous melanomas on small to medium size CMN are expected to have a similar prognosis as other conventional cutaneous melanomas, especially when similar to those arising on non-congenital nevi. Several studies have shown better overall prognosis, but mainly related to earlier detection and younger population than *de novo* melanomas[45,47].

Treatment depends on the stage of the disease; wide surgical excision is recommended for any case with local disease (stage in situ, I or II according to the 8th version AJCC staging system) [67]. Surgical excision is also generally proposed for stage III (lymph node involvement or in transit metastasis). Systemic adjuvant therapy with immune-checkpoint inhibitors is recommended for advanced or high-risk disease; stages IIB, IIC, and III after surgical treatment. When the disease is disseminated in regional lymph nodes or distant metastasis, systemic therapy is the standard of care. Immune-checkpoint inhibitors or in the case of a targetable mutation being identified, target therapies (BRAF and MEK inhibitors)[68,69].

Patients affected by large/giant or multiple CMNi need an individually tailored follow up from birth. A multidisciplinary team is recommended, including dermatologists, neuropediatricians, psychological support staff, and depending on the area involved also orthopediatricians, ophthalmologists, and plastic surgeons[70]. To detect early melanoma development, clinical and radiological follow-up is recommended, similar to other cutaneous melanomas according to the stage [68,71]. Periodic MRI of the central nervous system is required in symptomatic or in neurocutaneous syndrome.

Melanomas developed on giant CMNi, frequently arising in prepubertal patients have a poor outcome, worse than melanomas developed on acquired nevus and even *de novo* melanoma[47,72]. Immune checkpoint inhibitors are the main therapeutic tool, but are probably less effective since they usually show neither high mutation burden, nor ultraviolet radiation-fingerprint mutations (such as CC_TT). In addition, MEK inhibitors have not shown efficacy[72].

4. Conclusions

Large and giant CMNi are less frequent than small and medium size CMNi but the risk of developing a melanoma at prepubertal age is higher and potentially lethal. In addition, patients with large and giant CMNi have more morbidity especially due to CNS malformations, neurocutaneous melanosis syndrome, and melanoma development in the CNS.

All these data indicate the need to perform periodic clinical follow-up of these patients using non-invasive techniques. However, biopsies are necessary for histological evaluation of lesions that present new or sudden changes, to rule out the development of melanoma.

CRediT authorship contribution statement

Cristina Carrera: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Antonio Carrasco:** Writing – review & editing, Resources, Data curation. **Cristina Teixido:** Writing – review & editing, Supervision, Resources, Data curation. **Llucia Alos:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Asuncion Vicente:** Writing – review & editing, Supervision, Formal analysis, Data curation. **Daniela Massi:** Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. **Anna Szumera-Ciećkiewicz:** Writing – review & editing, Supervision, Data curation.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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