



## Melanocytic Lesions with Peripheral Globules: Proposal of an Integrated Management Algorithm

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**ABSTRACT** **Introduction:** A peripheral rim of globules represents a marker of the horizontal growth phase in nevi and is a common feature in children and adolescents. The observation of melanocytic lesions with peripheral globules (MLPGs) in adulthood deserves more attention, since melanoma may exhibit this feature, albeit rarely. Risk-stratified management recommendations considering a global clinical approach are still missing.

**Objectives:** To analyze current knowledge on MLPGs and propose an integrated management algorithm stratified for age groups.

**Methods:** We conducted a narrative review of current published data on MLPGs, analyzing clinical dermoscopic and confocal distinguishing features of melanoma from benign nevi.

**Results:** The risk of finding a melanoma when removing an MLPG increases with age, especially in people >55 years old, and is significantly higher in the extremities, head/neck and in case of a single asymmetrical lesion, ≥6 mm in diameter. Dermoscopic features associated with melanoma diagnosis include atypical peripheral globules, asymmetrical distribution, multiple rims as well as the reappearance of globules after prior loss. In addition, wide blue-grey regression areas, atypical networks,

eccentric blotches, tan structureless peripheral areas and vascularization are atypical dermoscopic features. Confocal worrisome findings are represented by pagetoid cells within the epidermis, architectural disarrangement and atypical cells of the dermo-epidermal junction with irregular peripheral nests.

**Conclusion:** We proposed a multi-step age-stratified management algorithm integrating clinical, dermoscopic and confocal findings that may increase the early recognition of melanoma and avoid surgical excision of benign nevi.

## Introduction

A dermoscopic subset of melanocytic lesions is characterized by the presence of round to oval globules regularly distributed at the edge of the lesion, representing a marker of the horizontal enlargement with a mean growth rate of  $0.25\text{mm}^2/\text{month}$  [1,2]. A decreased density or a complete disappearance of peripheral globules has been associated with a stabilization of nevi, with an estimated median time of growth cessation of 58.6 months (4-5 years) [1,3]. Enlargement of nevi is commonly observed in children and adolescents with a linear age-related prevalence reduction [3,4]. The common approach towards melanocytic lesions with peripheral globules (MLPGs) in patients younger than 35 years is conservative, not requiring interventions, as regards their benign clinical behavior [2,3]. The occurrence of MLPGs in adulthood and the elderly is infrequent and requires a cautious approach, since change over time represents a suspicious feature [3]. Furthermore, peripheral globules may also be detected, albeit rarely, in melanoma [3,5]. In 2007, the International Dermoscopic Society recommended that MLPGs exhibiting asymmetry of structures within the lesion should be closely monitored or excised, regardless of age [6]. Afterwards, it has been suggested to monitor MLPGs in the absence of other dermoscopic melanoma-specific criteria beyond the age of 30, considering instead surgical excision or close follow-up for those over 50 [3].

Reflectance confocal microscopy (RCM) allowed the accurate definition of globules as junctional clusters of melanocytes protruding into dermal papillae, or widening the interpapillary space, at the edge of the lesions with a perfect correspondence to histology [7]. Consecutive confocal evaluations of MLPGs in adults supported the dynamic evolution of this process, through an eccentric elongation of junctional clusters with narrowing of their shape, associated with a centrifugal extension [7].

Recent studies have been focused on the clinical approach to MLPGs, providing further insights into MLPGs, however heterogeneous management strategies have been proposed and common practical indications are still missing [5, 8-12].

## Objectives

The main aim of this manuscript is to critically review the current published data on MLPGs and to provide an integrated clinical, dermoscopic and confocal management algorithm stratified for age groups, resulting in a more appropriate and individualized management strategy.

## Methods

### Search Strategy

To identify eligible studies, a comprehensive search was conducted using PubMed electronic database with the following terms: “dermoscopy (MeSH)”, “dermatoscopy (MeSH)”, “confocal microscopy (MeSH)”, “melanocytic lesions (MeSH)”, “melanoma (MeSH)” and any one of the terms “peripheral clods (MeSH)”, “peripheral globules (MeSH)” published in English. The main search and the screening of titles and abstracts were completed independently by two reviewers (SC and LC). The manual search was concluded by the perusal of the reference sections of all relevant articles. All studies identified as relevant were analyzed and included. Case reports aiming to describe singular observations or written in non-native English language were excluded.

## Results

### Search Results

We completed a literature review by searching the electronic database PubMed until 1 December 2021, for all relevant records. A total of 125 articles were retrieved in the data synthesis: 120 were excluded due to being duplicated (among MeSH terms), not written in English, and not relevant (not related to melanocytic lesions). Finally, a total number of 5 studies were included and analyzed, and their main features are summarized in Table 1.

### Age and Clinical Data

The impact of patient age on clinical decision-making for MLPGs is well acknowledged but different thresholds and suggestions have been proposed [5,8-11]. Williams *et al*

**Table 1. Included studies on melanocytic lesions with peripheral globules.**

Study	Study design	Participant's age	No. of cases
Williams et al. 2020	Retrospective study	>20 yo	95 nevi 4 MM
Ribero et al. 2020	Retrospective study	35-85 yo (median age 49)	412 nevi 45 MM - 19 in situ - 26 invasive
Reiter et al. 2021	Cross-sectional, retrospective study	2- 85 yo (median age of MM=50 yo, median age of nevi=34 yo )	178 nevi 115 MM
Pampín-Franco et al. 2021	Prospective study, high risk patients	19-73 yo (median age 42 yo)	151 nevi 3 MM - 3 invasive
Carbone et al. 2021	Prospective study, high-risk patients	16-79 yo (median age 41 yo)	116 nevi 19 MM - 5 in situ - 14 invasive

MM= malignant melanoma, yo= years old

observed all confirmed cases of melanoma (4/99, 4.0% of MLPGs) in adulthood, specifically in individuals aged 30, 35, 40 and 55, without difference in the proportion of malignancy, when dichotomizing by age 50 (5.3% vs 3.9%,  $p=1.0$ ) [11]. Conversely, Ribero *et al* observed 9.8% of MLPGs (45/457) being melanomas (age ranged from 35 to 85 years) with a dramatic increase of frequency in patients >55 years old (10/69, 15%) [5]. Two other studies found a positive trend between histologically proven dysplastic nevi and melanoma with patients' ages, even though without statistical significance [9,10]. In particular, Reiter *et al.* reported a diagnosis of melanoma for 39.2% (115/293) of total MLPGs with an average age of 50 years old (range 20-85 years old), and more than half of cases (68%) being younger than 60 years old [9]. A lower percentage of melanoma (1.9%, 3/154 MLPGs) was observed by Pampín-Franco *et al* with 49.5 years old estimated as the median age of malignancy in high-risk patients, defined as patients under digital dermoscopic surveillance for atypical mole syndrome and/or personal or familial history of melanoma [10]. In a similar selected population of high-risk adults, Carbone *et al* reported a higher rate of malignancy with 19 melanomas in 135 MLPGs (14%) with a mean age of 49.8 years old and 10% of cases occurring even in patients under 30 years old [8] (Table 1).

Concerning the anatomic site of MLPGs, the most common location was the torso and especially the back [5,8-10], while the risk of finding a melanoma when removing an MLPG resulted significantly higher in the extremities and head/neck [5,9]. A gender prevalence of MLPGs was largely not reported except for two studies with controversial results

[5, 8-11]. In addition, Pampín-Franco *et al.* reported an average size of MLPGs of 4.1 mm with a significant association with the diagnosis of melanoma in lesions  $\geq 6$ mm in diameter, as well as in MLPGs showing asymmetry in two axes [10]. Moreover, the authors highlighted that multiple MLPGs in a single patient were statistically less likely to be diagnosed as melanoma [10] (Table 2).

### Dermoscopy

The morphology and distribution of peripheral globules along with the presence of additional atypical features in MLPGs was recently investigated, with the objective to identify specific structures indicating a diagnosis of melanoma [8-11].

Dermoscopic findings that support a diagnosis of melanoma included atypical globules (irregular in shape, size or color) and/or their asymmetrical distribution. Completely circumferential atypical globules are reported to have the highest risk of being melanoma, followed by focal circumferential atypical globules and focal circumferential typical globules [9]. Globules distributed in more than a single rim (tiered) and departing within the edge of a lesion were found to be more frequently observed in melanoma rather than nevi, as were peripheral globules covering less than 25% of the entire circumference (especially in case of <1-history) [9,10]. In addition, the reappearance of peripheral globules after their previous disappearance has been also related to a diagnosis of melanoma, and this finding is in contrast with the expected evolution of MLPGs [2,10].

Other relevant diagnostic clues suggesting melanoma were the presence of blue-grey regression areas (especially when involving a large part of an MLPG, >50%) and atypical

**Table 2. Clinical, dermoscopic and confocal criteria associated with the diagnosis of melanoma showing peripheral globules.**

Clinical Data	Dermoscopy	RCM
Extremities and head/neck	Regular PG with at least 2 melanoma-specific structures	Epidermis
Single lesion rather than multiple MLPG	OR	Pagetoid cells (roundish or dendritic)
≥6 mm diameter	≥2 of the following findings	DEJ
Asymmetry in two axes	PG in less than 25% of the circumference with 1 year history	Unspecific pattern
	Reappearance of PG	Non-edged dermal papillae
	PG irregular in size, shape, or color	Architectural disarrangement
	Atypical and/or asymmetric distribution of PG	Atypical thickenings
	Blue-grey regression structures involving >50% of the lesion	Atypical cells
	Vascularization	Peripheral dense irregular (sparse) nests
	Off-center blotches	
	Peripheral tan structureless areas	

rcm= reflectance confocal microscopy, mlpg= melanocytic lesions with peripheral globules, pg= peripheral globules, dej= dermal-epidermal junction

networks [10]. Eccentric blotches, tan structureless peripheral areas and vascularization were also considered worrisome features [10,11]. In presence of a regular distribution of peripheral globules, at least two melanoma-specific criteria were considered indicative of malignancy by Reiter *et al*, while for Williams *et al* a single melanoma specific-structure was sufficient, although such circumstance was observed in more than half of nevi and in all melanoma cases (Table 2) [9,11].

Remarkably, the risk of an MLPG being a melanoma remains not negligible even for lesions that exhibit only peripheral regular globules without additional worrisome dermoscopic criteria [5].

### Confocal Microscopy

*In-vivo* confocal evaluation of MLPGs, with a detailed analysis of global architecture and cytological aspects, was performed in two studies [8,10]. Classical melanoma-specific findings were detected in 100% of malignant MLPGs [8,10]. In detail, the presence of intraepidermal pagetoid cells (roundish or dendritic in shape) was strongly related to the diagnosis of melanoma [10]. Moreover, architectural disarray of the dermo-epidermal junction (DEJ), unspecific pattern or non-edged dermal papillae, and atypical junction thickening represented confocal findings more frequently observed in malignant lesions. Atypical cells at the DEJ, especially when multiple, along with the presence of irregular and sparse peripheral nests with an evident cleft, were also reported as being associated with histologically proven melanomas (Table 2) [8,10]. No lesions showed true cerebriform nets. Inflammatory cells and melanophages at the

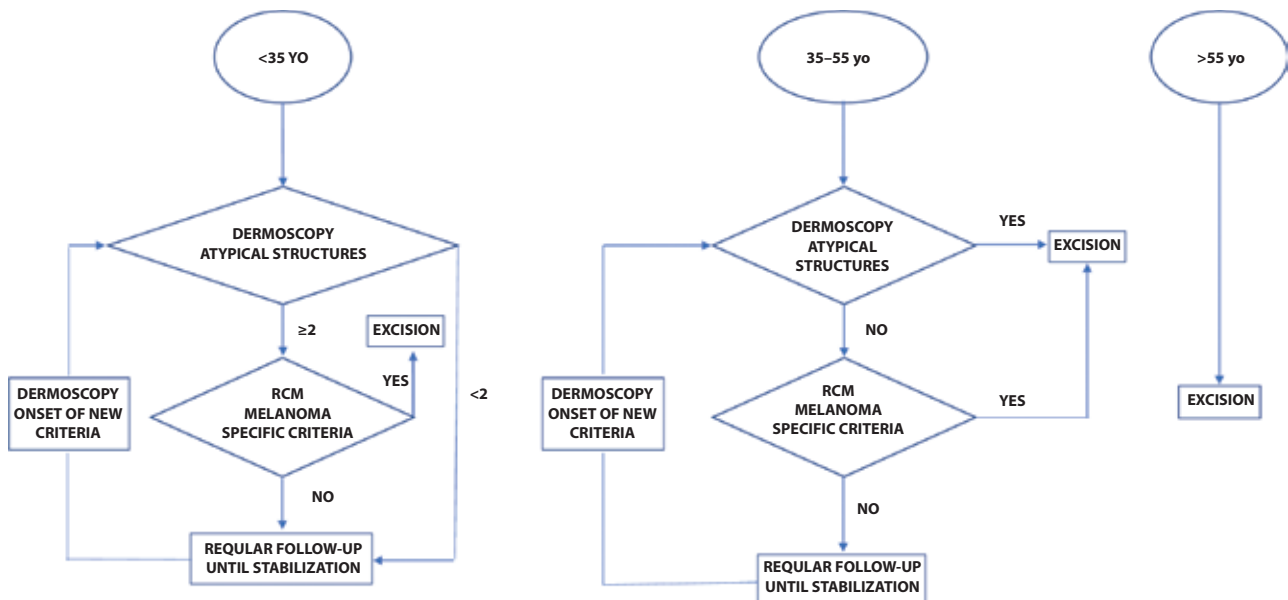
papillary dermis were seen either in benign nevi or in melanomas [10].

### Proposal of an Integrated Management Algorithm

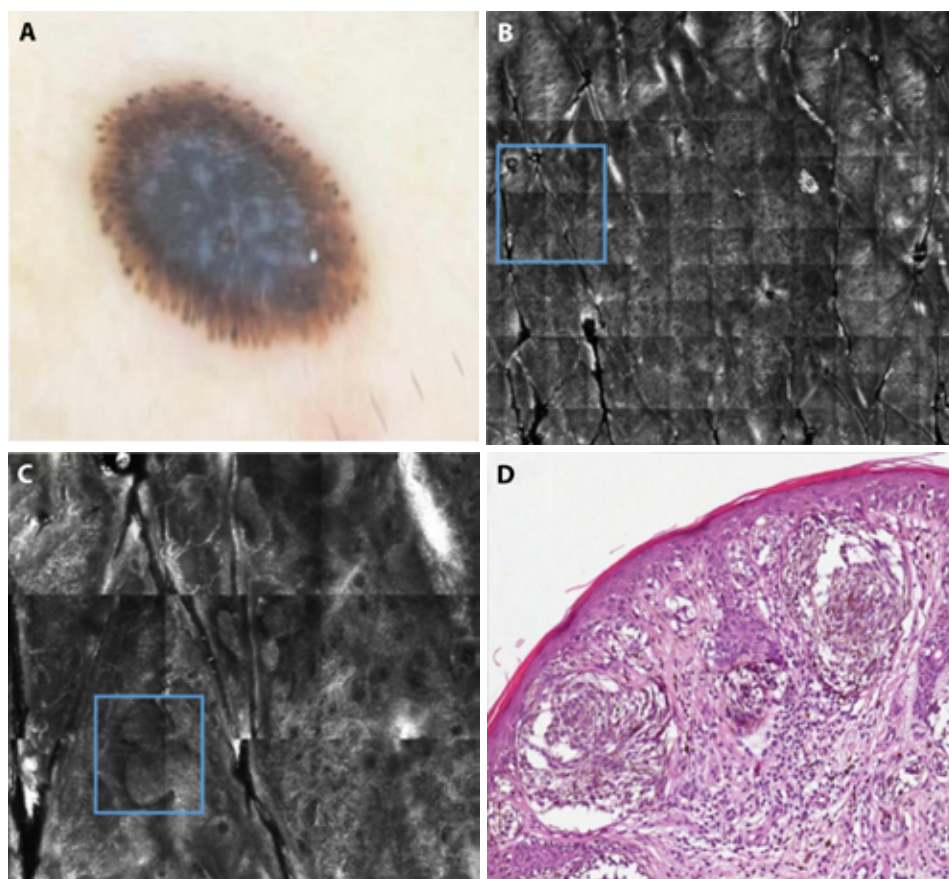
Herein we propose a flowchart algorithm for individualized management of MLPGs considering clinical, dermoscopic and confocal criteria, with the aim to identify melanomas at an early stage and to reduce as much as possible the unnecessary surgical excision of benign nevi (Figure 1). The proposed algorithm is outlined to provide risk stratification and includes the following steps:

**MLPGs in Patients <35 Years Old:** regular dermoscopic monitoring is recommended for lesions showing an organized rim of globules with a reticular, globular, or mixed central pattern. A decreased density of peripheral globules resulting in total disappearance, in an overall period of 4-5 years, is expected. This clinical evolution allows the interruption of follow-up surveillance at the end of the process. We suggest performing RCM in MLPGs when at least two atypical dermoscopic structures are detected, as we still consider the very low percentage of melanoma exhibiting this pattern in patients younger than 35 years old. In the absence of cyto-architectural atypia a dermoscopic follow-up can be extended whereas in presence of confocal melanoma-specific criteria, surgical excision is recommended (Figure 2). MLPGs showing ≥2 new-onset atypical dermoscopic structures during dermoscopic surveillance should be further investigated by means of RCM and follow the same recommendations.

**MLPGs in Patients 35-55 Years Old:** In this age group, MLPGs should be managed with more caution, with a careful assessment of dermoscopic features: if any atypical

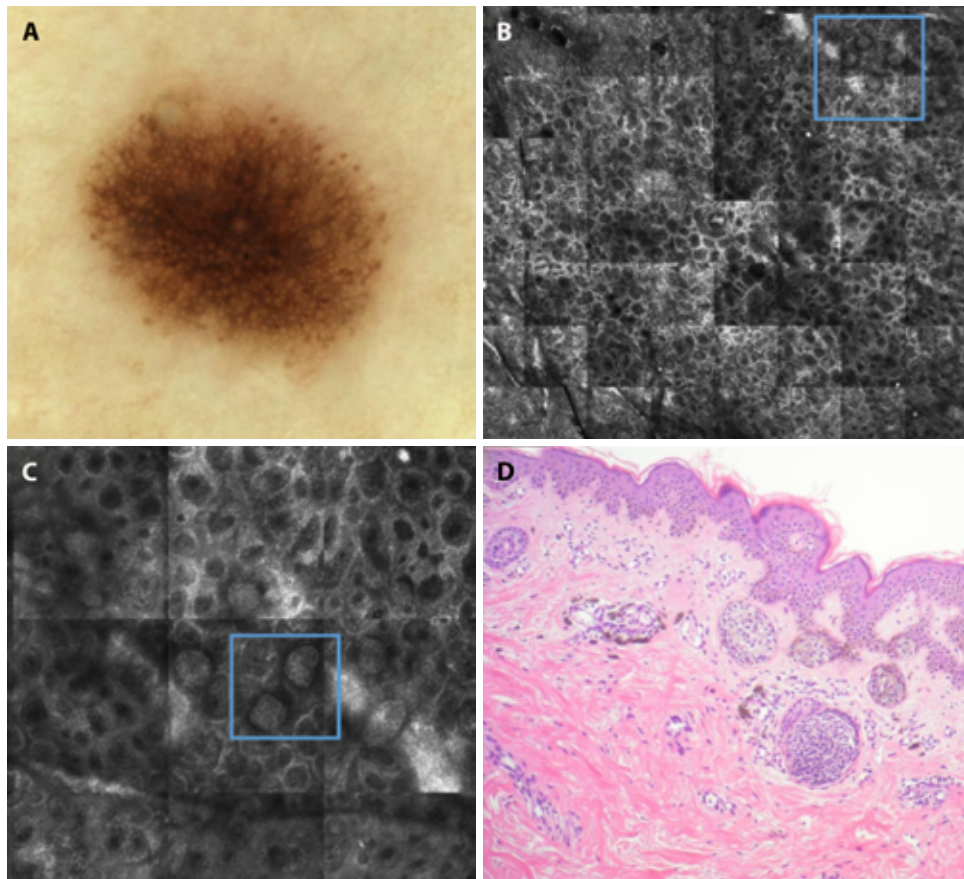


**Figure 1.** Our proposed algorithm for the clinical management of melanocytic lesions with peripheral globules, including dermoscopic and confocal findings in different age groups.



**Figure 2.** Invasive melanoma (Breslow 0.9 mm) on the upper back of a 33-year old man: dermoscopy (a), RCM (b,c) and histology (d). Irregular blotches, shiny white streaks and blue-whitish veils are observed at dermoscopy beyond a regular distribution of peripheral globules (a). A confocal section of the dermal-epidermal junction displays dendritic cells and sparse nests (blue squares) (b, low magnification; c, high magnification) corresponding to the epidermal spreading of melanocytes and disorganized nests seen on histology (d) [Haematoxylin and eosin stain, original magnification x200].





**Figure 3.** Nevus on the right leg of a 46-year-old woman: dermoscopy (a), RCM (b,c) and histology (d). Peripheral globules are symmetrically organized at the edge of the lesion (a), corresponding to dense melanocytic nests (blue squares) located at the dermal-epidermal junction and papillary dermis upon confocal view at low (b) and high (c) magnification. A ringed pattern composed of edged dermal papillae is observed in the central area (b). Junctional melanocytic nests are observed at histopathology (d) [Haematoxylin and eosin stain, original magnification x200].

dermoscopic structure is detected, surgical excision is recommended. In addition, we suggest performing RCM evaluation also in the absence of melanoma-specific dermoscopic criteria (Figure 3). Confocal cyto-architectural irregular features require surgical excision of the lesion, while a regular follow-up is suggested in case of reassuring findings. During the follow-up period, surgery is recommended where new atypical dermoscopic criteria are observed.

The decision to perform RCM in the range of 35-55 years old, even in presence of reassuring dermoscopic criteria, is due to the still not negligible risk of a regular MLPG being a melanoma. Indeed, 50 years old was assessed as the median age of patients with a proven histological diagnosis of melanoma in different studies [9,10] and confocal evaluation has been demonstrated to disclose irregular/atypical findings with a 100% sensitivity for the diagnosis of MM [8,10].

**MLPGs in Patients >55 Years Old:** in this age group, the suggested management is surgical excision in all cases. While growth markers of melanocytic lesions are expected in young adults, the observation of MLPGs in the elderly represents a

warning signal and the chance of an MLPG being a melanoma exhibiting only organized peripheral globules without other worrisome dermoscopic features represents a concrete risk after 55 years old [5].

### Limitations

A limitation of this work is the inclusion of different studies with heterogeneous methodological cohorts and interventions, with no age-group standardisation. In addition, it should be considered that non-proven histologic MLPGs were not considered in the studies, and this may have contributed to a realistic underestimation of benign nevi exhibiting peripheral globules. This scenario may be due to the most common approach of favoring a surveillance program of MLPGs over time, under 35 years old in daily practice. Lastly, data synthesising dermoscopic and confocal criteria were retrieved from a small number of studies, and larger prospective datasets are needed to validate the utility of the proposed algorithm. The suggested management indications should be interpreted with caution and individualized for every single patient.

## Conclusions

MLPGs are frequently seen in daily practice and represent a clinical challenge requiring the most appropriate management for individual patients. Herein we propose a multi-step and age-based management algorithm based on current published data integrating clinical, dermoscopic and confocal findings, in order to increase the early recognition of melanoma and avoid surgical excision of benign lesions.

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