REVIEW ARTICLE

Longitudinal Melanonychia as a Rare Sign of Invasive Squamous Cell Carcinoma: Case Report and Systematic Review

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A 50-year-old male presented with 4-month history of longitudinal melanonychia on the fourth digit of his right foot. A nail matrix and bed biopsy was performed, which led to the diagnosis of invasive well-differentiated squamous cell carcinoma. Immunohistochemical analysis demonstrated positivity for P16 and P40. Longitudinal melanonychia may be a diagnostic challenge, as it can be associated with both benign and malignant conditions. Given the potential for locally aggressive behaviour, squamous cell carcinoma should always be considered in cases of longitudinal melanonychia. A systematic review was conducted in order to analyse all documented cases of invasive squamous cell carcinomas that presented as longitudinal melanonychia, highlighting any associated clinical, dermoscopic, histological, and immunohistochemical characteristics potentially useful for an early identification of this neoplasm.

Key words: longitudinal melanonychia; squamous cell carcinoma; systematic review; differential diagnosis; dermoscopy.

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Melanonychia without other nail alterations has been described as a rare manifestation of subungual squamous cell carcinoma (SCC), either *in situ* (Bowen's disease) or invasive (1). Although rare, these tumours are the most common malignant neoplasms of the nail unit (2). Subungual Bowen's disease presenting as longitudinal melanonychia seems to be more frequent when compared with its invasive variant (3).

We describe a case of longitudinal melanonychia with diagnosis of subungual invasive SCC. We analysed all previous reports with similar clinical and histopathological features, also highlighting dermoscopic and immunohistochemical features.

CASE REPORT

A 50-year-old male presented with a longitudinal melanonychia on the fourth digit of his right foot, which had been present for about 4 months. The brown band involved approximately half of the nail plate and appeared darker on its lateral side. The pigmentation extended to the surrounding cuticle. The nail plate appeared intact, with no signs of onychodystrophy, onychorrhexis, onychomadesis, or onycholysis.

Dermatoscopic examination of the nail band revealed multiple irregularly pigmented and thick parallel lines, with a brown background that was darker on the lateral side of the band, gradually fading towards its medial portion (**Fig. 1**).

The patient reported a history of regular, annual dermatological check-ups, no family history of skin cancers, and an unremarkable medical history with no current medication use. He denied any recent trauma to the affected digit. Given these findings, a biopsy of the nail matrix and bed was performed for diagnostic assessment (**Fig. 2**A). Histological examination revealed an invasive well-differentiated SCC. Immunohistochemical analysis for human papillomavirus (HPV) showed positivity for P16 and P40 (Fig. 2B).

Ultrasound imaging of the regional lymph nodes was performed with no evidence of lymphatic involvement. Following radiographic evaluation of the distal phalanx, which revealed no bone involvement, a wide surgical excision was performed, allowing preservation of the distal phalanx. The excision was confirmed to be radical upon histological assessment.

SIGNIFICANCE

Longitudinal melanonychia may be a manifestation of invasive squamous cell carcinoma of the nail unit. By presenting a case report and conducting a systematic review of all documented cases of invasive squamous cell carcinomas of the nail presenting with longitudinal melanonychia, the authors tried to identify clinical, dermoscopic, histological, and immunohistochemical features in order to support its early detection.

MATERIALS AND METHODS

Study objectives

A systematic review was conducted with the aim of collecting and analysing all reported cases of invasive SCC which presented as longitudinal melanonychia.

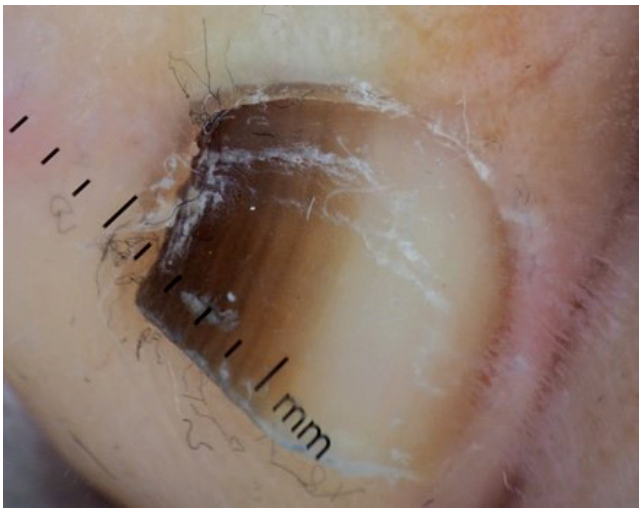

Fig. 1. Dermoscopy image showing a longitudinal melanonychia band involving approximately half of the nail plate of the fourth toe of the patient's right foot.

Specifically, we intended to assess and define the main clinical, dermoscopic, histological, and immunohistochemical features of this neoplasm for its most exhaustive characterization as possible. This review aims to support early diagnosis as well as differential diagnosis with regard to clinically similar entities.

Literature search and selection criteria

A widespread search was performed across multiple electronic databases, including MEDLINE (via PubMed), Scopus, and Embase, with the last search conducted on 21 March 2025. For the search we included the following keywords: "squamous cell carcinoma", "SCC", "longitudinal melanonychia", "melanonychia", "pigmented band", and "nail pigmentation". Boolean operators (AND, OR) were applied to refine the search.

Manuscripts were included if they reported either single cases or series of patients with invasive SCC presenting with longitudinal melanonychia. No restrictions were placed on the year of publication. Only articles published in English were considered. Case reports, case series, original research, and review articles were all eligible for inclusion, provided they contained relevant clinical or histopathological data. To ensure a comprehensive analysis, we also examined the reference lists of the selected articles to identify and include additional relevant studies. A data flow diagram is presented in **Fig. 3**.

Data extraction and analysis

In a first phase of this systematic review, the identified articles were screened by title and abstract, and full texts of potentially relevant studies were reviewed analytically. Reference lists of included articles were also manually searched to identify additional relevant studies.

RESULTS

Selection of studies

The initial search identified 221 articles. After removing duplicates, 117 unique articles remained for screening. Twelve articles were selected based on evaluating their titles and abstracts. An additional relevant case was retrieved from the reference list of 1 of the included studies. Ultimately, 7 studies were included in the final analysis, with a total of 11 patients (3–8).

All the results and detailed data of this review are summarized in **Table I**, where we included also the case described here, thus overall we assessed 12 cases.

Detailed information for each excluded study after reading the full text is provided in **Table II**.

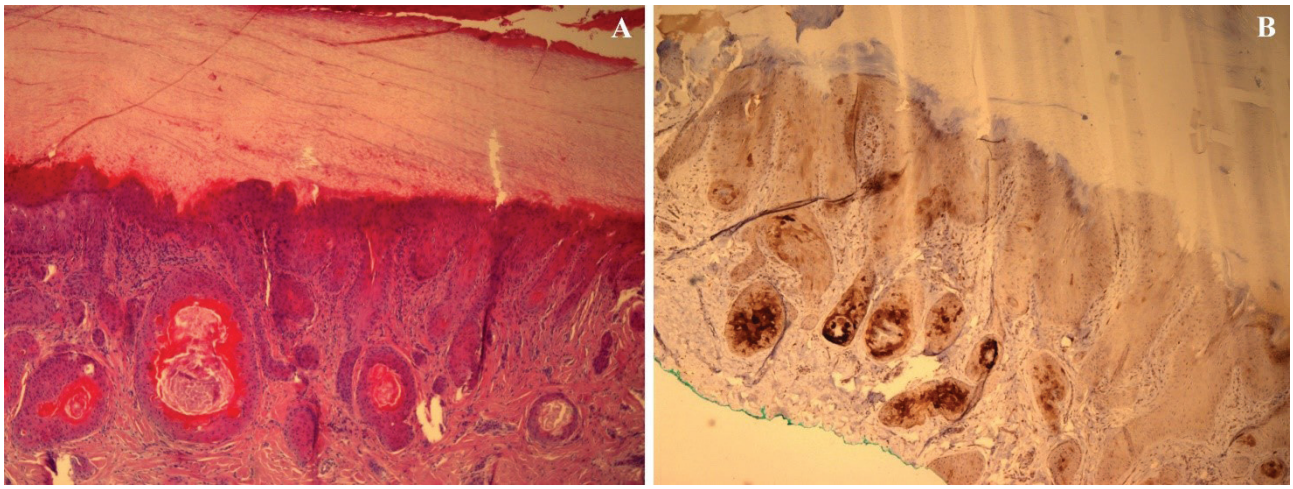

Fig. 2. (A) Proliferation of atypical keratinocytes invading into the dermis with a nest pattern, showing areas of keratinization (keratin pearls) and squamous eddies. Haematoxylin-eosin, original magnification x4; (B) P16 immunohistochemistry showing focal staining, original magnification x4.

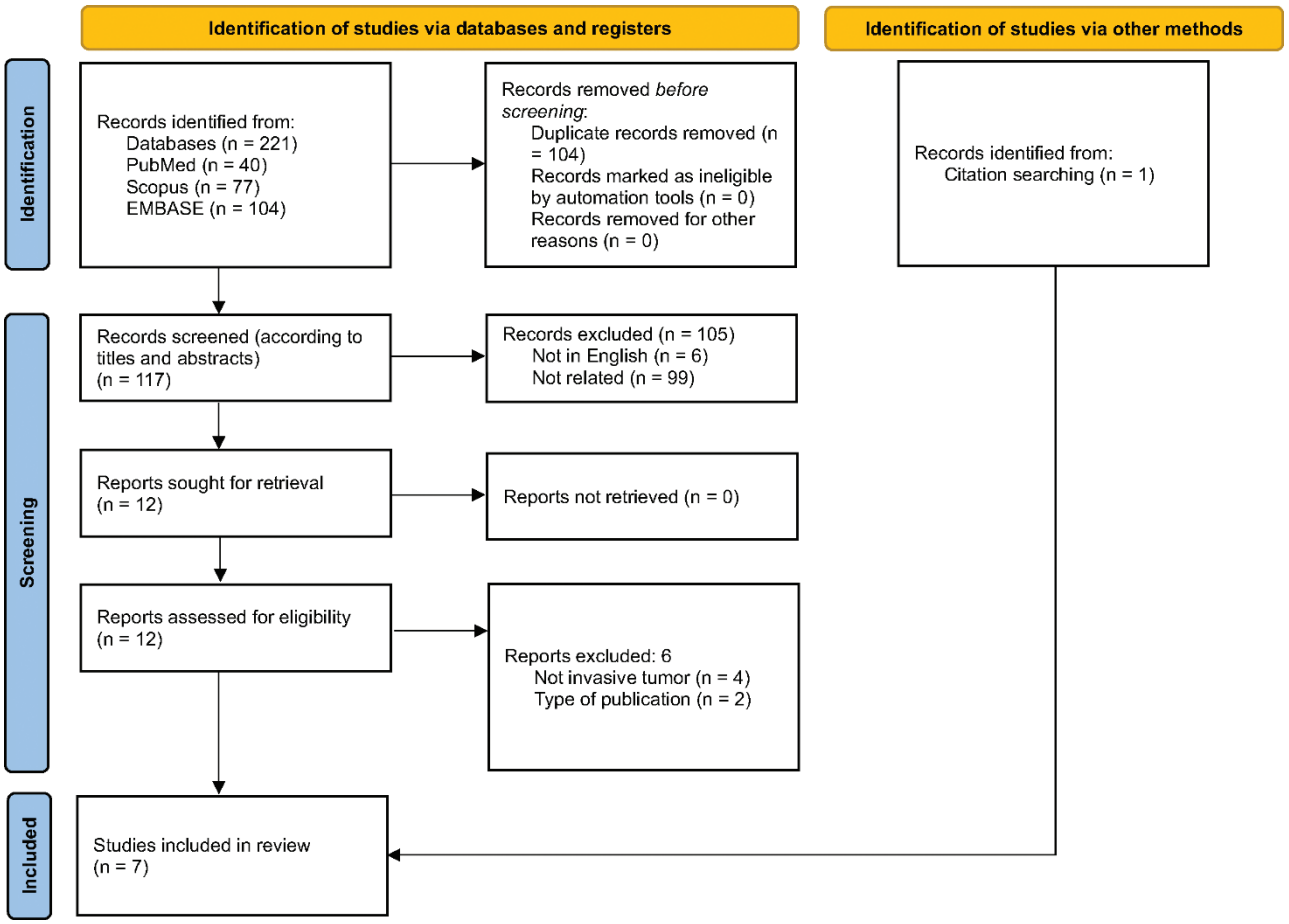

Fig. 3. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Table I. Cases of invasive squamous cell carcinoma presenting with longitudinal melanonychia

Case no.	Authors (year)	Age, years/sex	Digit	Clinical description	Dermoscopy	Histology/tumour thickness (mm)	Immunohistochemistry
1	Dalle et al. (2007) (4)	50/M	1RF	LM, subungual tumour	Not specified	Invasive SCC/0.6	Not specified
2		73/M	5LH	LM		Invasive SCC/0.9	
3		39/F	2RH	LM		Invasive SCC/0.5	
4		63/F	1RH	LM		Invasive SCC/0.8	
5		56/F	1LF	LM, onycholysis		Invasive SCC/0.5	
6	Fernandes Massa et al. (2013) (9)	47/M	1RF	LM with irregular thick lines, colour ranging from light to dark brown	Linear pattern on the distal matrix and globular pattern on the proximal nail bed	Well-differentiated infiltrated SCC/upper dermis	Not specified
7	Lecerf et al. (2013) (5)	34/M	3RH	Warty appearance with LM	Not specified	Invasive SCC/1.5	Not specified
8	Ishida et al. (2014) (6)	59/F	1RH	Circumscribed and uniform brownish LM, 2 mm in width	Not specified	Pigmented SCC/superficial dermis Melanin pigment within the cytoplasm of the neoplastic cells and a few dendritic melanocytes within the tumour nests	Dendritic melanocytes: positive for S-100 protein and Melan-A Neoplastic squamous cells: HPV not detected
9	Gatica-Torres et al. (2016) (7)	20/M	2LH	Grey LM, 4.5 mm in width, with mild subungual hyperkeratosis	Curved grey melanonychia with small darker globules	Pigmented SCC/full thickness atypia of the nail bed	Not specified
10	Nojima et al. (2017) (8)	80/F	1RH	Grey to black LM, 5 mm in width, with a subungual keratotic tumour pigmented at its periphery	Grey to black band On the lateral side: lighter colour and a white to yellow area with surface scales Subungual tumour: surface scales on a white to pink background and grey to black dots and areas at the periphery	Pigmented SCC/papillary dermis Dense melanin granules in tumour nests and in the corresponding cornified layer at the proximal edge of the tumour	Positive for AE1/3 and 34βE1 HPV not detected
11	Lee et al. (2022) (3)	84/M	3RH	LM, wider proximally than distally; mild-to-moderate hyperkeratosis on the lateral side	Not specified	Invasive SCC/0.1	Not performed
12	Our case (2025)	50/M	4RF	LM with irregular thick lines, half-nail width	Heterogeneous bands, darker on the lateral side	Invasive well-differentiated SCC	Positive for HPV P16 and P40

F: female; LF: left foot; LH: left hand; LM: longitudinal melanonychia; M: male; RF: right foot; RH: right hand; SCC: squamous cell carcinoma.

Table II. List of excluded studies and the reasons for their exclusion

No.	Author	Year	Reason for exclusion
1	Harwood et al. (18)	2008	Squamous cell carcinoma was *in situ*
2	Hernandez et al. (19)	2015	Paper was an abstract of poster
3	Serret et al. (20)	2018	Squamous cell carcinoma was *in situ*
4	Ning et al. (21)	2020	Squamous cell carcinoma was *in situ*
5	Sanchez-Carpintero et al. (22)	2020	At the time of diagnosis, squamous cell carcinoma was *in situ*
6	Puyana et al. (23)	2022	Paper was an abstract of poster

Characteristics of the included studies

The included papers were published between 2007 and 2022 and consisted of 5 case reports and 2 retrospective studies, which were included as they specifically reported cases of nail invasive SCCs presenting with melanonychia, so their data were consistent with the inclusion criteria.

Details of patient characteristics

Patient age ranged from 20 to 84 years, with a slight predominance of male cases (7 out of 12). Hand fingers were the most affected digits (8 out of 12).

Clinical features

Among the cases analysed, the clinical presentation of nail SCCs, detailed in Table I, exhibited considerable variability, particularly in respect of the width and pigmentation of longitudinal melanonychia. The thickness of melanonychia was measured and reported in 3 of the 11 cases described, with widths of 2 mm (6), 4.5 mm (7), and 5 mm (8), respectively. Pigmentation patterns were reported in 4 out of the 11 cases described and were heterogeneous too. In more detail, they included well-circumscribed, uniformly brownish bands (6) or irregular thick lines varying from light to dark brown (9) or grey (7) and grey-to-black (8) longitudinal melanonychia.

In 2 single reports, longitudinal melanonychia was accompanied by a subungual tumour. In more detail, in 1 case, the tumour appeared warty (5), while in the other it was described as a keratotic, flat-elevated mass with peripheral pigmentation (8).

Other reported clinical features included subungual hyperkeratosis (7), laterally located hyperkeratotic changes (3), and onycholysis (4).

Dermoscopic features

In addition to the case observed by us, dermoscopic descriptions were provided in 3 further cases among the 11 reported in the scientific literature (see Table I). Fernandes Massa et al. (9) reported a melanonychia striata with irregular longitudinal lines, ranging from light- to dark-brown. A globular pattern on the proximal nail bed and a linear pattern on the distal matrix were noted. In the case described by Gatica-Torres et al. (7) the dermoscopic observation revealed a curved grey melanonychia with small darker globules. Nojima et al. (8) described a longitudinal melanonychia with grey to black bands, lighter on the lateral nail side. The lateral portion of the nail showed a white to yellow area with desquamation. A subungual tumour was also present, characterized by surface scaling on a white to pink background, with grey to black dots and patches at the periphery.

Histopathological features

Specific histopathological features were not consistently reported across all cases. Some reports provided the depth of tumour invasion, which ranged from a minimum of 0.5 to a maximum of 1.5 mm (5, 10). In other cases, the histological depth of tumour invasion was specified. One report described full-thickness involvement of the nail bed (7), while another report found cancer invasion limited to the upper dermis, with no epidermal alterations, consistent with a well-differentiated tumour (9).

Ishida et al. were the first to describe, in a case of SCC infiltrating the papillary dermis, the presence of melanin within the cytoplasm of neoplastic squamous cells and dendritic melanocytes within the tumour nests, correlating with the clinical presentation of melanonychia (6). Similarly, Nojima et al. observed dense melanin granules within both the tumour nests and the cornified layer at the proximal margin of the lesion (8). Finally, Lee et al. reported increased benign basal melanocytes and melanin granules (3).

Additional features

Immunohistochemical analysis was reported in 5 cases, showing positivity for AE1/3, 34βE12 in neoplastic squamous cells (8), while dendritic melanocytes were

Table III. Principal differential diagnosis of longitudinal melanonychia

	Clinical features				
Diagnosis	Colour	Size	Additional features	Typical age of onset	Dermoscopic features
SCC	Uneven, possible mixture of light and dark brown or of grey and black	2–5 mm	Possible concurrent hyperkeratosis, subungual tumour, onycholysis	54.6 years (mean age based on the present systematic review)	Irregular lines, heterogeneous colour; non-specific pattern, clusters of dot-like or glomerular vessels, islands of whitish scales
Melanocytic nevus	Homogeneous, variable from light to dark brown to black	Narrow and stable in time	No nail dystrophy	Children and young adults	Regular parallel lines; uniform spacing, colour and thickness
Melanoma	Dark brown to black	Broad, usually widening	Irregular band borders, Hutchinson's sign, nail dystrophy, subungual nodule	50–70 years	Irregular lines in terms of colour, spacing, thickness, parallelism; grey to black background

SCC: squamous cell carcinoma.

positive for S-100 protein and Melan-A in a single case (6). HPV was evaluated in 2 cases in addition to the present one (6, 8), with only ours showing positivity for HPV P16 and P40.

DISCUSSION

The aim of this systematic review was to analyse in depth all cases of invasive SCC described in the literature, in addition to the case described by us, which presented as longitudinal melanonychia.

Melanonychia refers to the presence of a black or brown pigmentation of a nail. When it appears as a longitudinal band, it is known as longitudinal melanonychia, which is typically the most frequent clinical manifestation of nail melanotic or melanocytic lesions, but it can also be correlated to other underlying causes, which may be difficult to differentiate clinically (2).

Melanotic macule is the most common cause of melanonychia in adults. It is clinically characterized by a flat macule and dermoscopically as a homogeneous greyish band. Nail matrix melanocytic nevi are often seen in children and young adults and they appear as longitudinal parallel and homogeneous pigmentation of the nail, with a colour ranging from light to dark brown to black. Dermoscopy usually reveals longitudinal parallel lines with regular spacing and thickness (11).

In any adult with longitudinal melanonychia involving a single finger, it is imperative to take melanoma into consideration. Nail matrix melanoma usually presents as a gradually expanding dark-brown to black band, with blurred and irregular lateral borders, progressing to nail plate dystrophy in advanced stages. Pigmentation of the nail fold cuticle and the surrounding skin, known as Hutchinson's sign, can be observed (11). Dermoscopic features suggestive of nail melanoma include a black to grey background with longitudinal lines that are irregular in thickness, spacing, colour, or parallelism (2). The main clinical and dermoscopic features of the aforementioned differential diagnoses of longitudinal melanonychia are summarized in **Table III**.

Nail SCC has a slow, progressive, and usually indolent course. Its clinical features are quite heterogeneous, although it most commonly presents as a warty mass that leads to gradual onycholysis. More rarely, it may appear ulcerative, nodular, or as a longitudinal erythronychia or melanonychia (1). In a Belgian retrospective study, different variants of subungual SCC were analysed. Most cases involved male patients (72.5%) and were *in situ* carcinomas (63%). The most common clinical presentation was the warty variant (47%), which was associated with longitudinal melanonychia in 11.8% of cases. No cases presented with isolated longitudinal melanonychia. Other clinical variants observed included onychopapilloma-like, fibrokeratoma-like, or onychomatricoma-like carcinomas (5). Only one of the 54 tumours of this retrospective series was included in our systematic review, as it presented with both longitudinal melanonychia and histological evidence of dermal invasion (with a depth of 1.5 mm).

From a clinical perspective, the 11 reported cases of invasive nail SCCs presenting as melanonychia, which were analysed in this review, exhibited considerable heterogeneity (see Table I). Based on the available data, longitudinal melanonychia ranged in width from 2 mm to 5 mm (6–8). The observed pigmentation patterns were markedly heterogeneous too, varying from well-demarcated, homogeneously pigmented longitudinal bands (6) to irregular and variegated streaks (9). Their colours ranged from light to dark brown (9) and from grey to black (7, 8).

In addition to longitudinal melanonychia, other concomitant reported clinical features included subungual hyperkeratosis (7, 8) or the presence of a subungual tumour without a specific clinical description (4), or a subungual keratotic tumour with pigmentation at its periphery (8) and/or onycholysis (4).

Dermoscopic features of nail SCCs, regardless of tumour depth, include clusters of dot-like or glomerular vessels, islands of whitish scales, and hyperkeratotic structures. When associated with melanonychia, their dermoscopic pattern consists of broad streaks, usually light to dark brown in colour, with irregular shape and distribution (1, 12).

In the 3 cases of invasive SCC for which dermoscopic descriptions are available, the pigmentation patterns were quite different from each other. The colour ranged from light- to dark-brown (9) or from grey to black bands (8). In another case, a grey melanonychia with small darker globules was noted (7). In our case, dark-brown longitudinal streaks were observed on a lighter brown background.

Therefore, based on the currently limited evidence, dermoscopy does not appear to be a reliable tool for distinguishing SCC-associated melanonychia from that arising due to other aetiologies, including melanoma. As described by Fernandes Massa et al. (9), the possibility of using reflectance confocal microscopy, both *in vivo* and *ex vivo*, to assess the melanocytic or non-melanocytic nature of longitudinal melanonychia is of particular interest.

Our analysis identified 2 cases of longitudinal melanonychia characterized by grey pigmentation, which were described both clinically and dermoscopically (7, 8). These findings may be noteworthy in the context of the differential diagnosis with acral lentiginous melanoma presenting as longitudinal melanonychia. Acral lentiginous melanoma-associated melanonychia may also present as a band, typically broad and progressively widening, of grey or grey-black pigmentation (13).

Histopathology remains the gold standard for the diagnosis of nail unit SCCs (1). According to the selec-

tion criteria of this systematic review, all tumours considered were histologically infiltrative, as *in situ* forms were excluded. When reported, the infiltration thickness ranged from 0.1 to 1.5 mm (3–5). In the other papers infiltration was more frequently described as limited to the superficial dermis (6, 8, 9). In a single case a full thickness atypia of the nail bed was reported (7).

Interestingly, in the retrospective study by Lee et al. (3), a significant association was observed between the presence of longitudinal melanonychia and the depth of carcinoma invasion. Specifically, among the 6 SCCs presenting with longitudinal melanonychia, 5 were *in situ* and only 1 exhibited minimal dermal invasion (0.1 mm), whereas the remaining 14 cases without melanonychia showed significantly deeper invasion (mean 1.59 mm, median 1.75 mm). The authors hypothesize that a possible explanation for a more frequent association between longitudinal melanonychia and less invasive forms of nail SCC could be that melanonychia is more closely related to the hyperkeratotic subtype rather than the nodular variant. Indeed, according to the classification proposed by Dika et al. (14), nodular forms would have a greater thickness. A second hypothesis refers to the presence of HPV-related Bowen disease. In these cases, histological examination of nail Bowen disease associated with melanonychia has revealed an increased number of benign basal melanocytes and melanin granules. These hypotheses could account for the small number of invasive SCCs associated with melanonychia reported in the scientific literature so far.

As regards histology, the presence of longitudinal melanonychia could be explained by several findings. These include melanin within the cytoplasm of neoplastic squamous cells and dendritic melanocytes within the tumour nests (6), as well as melanin granules within both the tumour nests and the corresponding cornified layer (8) and increased benign basal melanocytes (3). The presence within a non-melanocytic tumour of non-neoplastic melanocytes has been referred to as so-called "melanocytic colonization" (6). The physiopathological basis on which SCCs may develop in conjunction with melanocytes or melanin accumulation remains unknown. A plausible hypothesis is that epithelial cells release signalling molecules that exert targeted effects on melanocytes. Keratinocytes physiologically secrete various growth factors – including stem cell factor (SCF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), endothelins, and nerve growth factor (NGF) – known to regulate melanocyte biology. It is therefore reasonable to postulate that neoplastic keratinocytes in pigmented SCCs may produce and release such factors, particularly SCF and endothelin-1, thereby promoting melanocytosis. SCF stimulates melanocyte proliferation by accelerating cell cycle progression, while endothelin-1 enhances melanogenesis and DNA synthesis. Moreover, inflammatory cytokines such as IL-1α and TNF-α may contribute to the upregulation of these factors in a tumour microenvironment, potentially explaining their enhanced expression in pigmented compared with non-pigmented SCCs. In a case of pigmented SCC of the oral mucosa, the immunohistochemical analysis for proliferating cell nuclear antigen (PCNA) was negative, indicating that the melanocytes were not in a proliferative state (15). This finding suggests that SCF and/or endothelin-1 might play a role in promoting melanocyte activation through mechanisms other than proliferation, such as enhanced melanogenic activity or increased cellular migration. However, these hypotheses do not explain a supposed higher incidence of striated melanonychia in *in situ* SCC when compared with invasive forms. Moreover, in our case there was no histological evidence of either melanocytic proliferation or melanin pigment accumulation. This suggests that melanonychia is not necessarily attributable to an abnormal accumulation of melanin within the epidermis or dermis. It is conceivable that, either partially or alternatively, melanonychia may arise from the aberrant presence of keratinous material.

SCC pathogenesis includes exposure to ionizing radiation, tobacco, trauma, arsenic, and immunosuppression. Moreover, there is increasing evidence of the role of human papilloma virus (HPV) in its development, in particular high-risk HPV 16. HPV16 has been found in 50% and 73% of cases of *in situ* and invasive nail unit SCC, respectively (1, 16). In the case described by us, positivity for P16 and P40 was reported. In most of the cases of nail SCCs that presented as melanonychia reported in the literature, immunohistochemical testing for HPV was not performed. It was conducted in 2 cases and was negative (6, 8). Nail unit SCCs associated with high-risk HPVs appear to be more locally aggressive than those not associated; they show higher recurrence rates, increased proliferative activity, and the possibility of metastasis (12). To our knowledge, our case is the first documented invasive subungual SCC presenting as longitudinal melanonychia with positivity for high-risk HPV. Determining whether a nail SCC is associated with HPV could be valuable for exploring alternative or complementary treatment options beyond surgery, such as HPV vaccination. So far, this approach has been considered successful in only 1 reported case of nail Bowen's disease (17).

Longitudinal melanonychia may represent a clinical manifestation, albeit rare, of nail unit SCCs, including invasive forms. This clinical presentation may mimic a melanocytic proliferation, making the differential diagnosis particularly challenging and jeopardizing the potential for conservative surgical management. Early recognition and timely intervention are essential to optimize outcomes and prevent unnecessary morbidity.

Invasive SCCs presenting with longitudinal melanonychia typically show heterogeneous irregular pigmented bands, ranging from light to dark brown and from grey

to black, and may not be accompanied by a subungual tumour, potentially delaying early diagnosis.

Given the clinical and dermoscopic overlap with both benign and malignant melanocytic conditions, it is essential to proceed with appropriate diagnostic investigations, in particular histopathological examination.

In conclusion, invasive SCCs should always be considered in the differential diagnosis of longitudinal melanonychia.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement: The patient in this manuscript has given written informed consent to the publication of his case photograph and details.

The authors have no conflicts of interest to declare.

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