



Dealing with Melanonychia

Antonella Tosti, MD,* Bianca Maria Piraccini, MD,* and Débora Cadore de Farias, MD[†]

Melanonychia describes a brown or black pigmentation of the nail plate caused by the presence of melanin. In this article, we review possible causes of melanonychia and discuss the main problems of management of patients with this condition. The goal in the management of melanonychia is early diagnosis of melanoma of the nail matrix and bed. Melanoma of the nail bed is also known as subungual melanoma. We discuss clinical, dermoscopic features that may help the clinician in selecting lesions that should have excisional biopsy and evaluate different options for the excision. Addressing melanonychia is still a difficult task, and the correct management of pigmented bands in children is far from established. Dermoscopy is possibly a useful tool but the real benefit of this technique, screening lesions to determine which ones need to be removed, remains to be proven.

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Melanonychia, a brown or black pigmentation of the nail plate caused by the presence of melanin, commonly appears as a longitudinal band (longitudinal melanonychia, LM) starting from the matrix and extending to the tip of the nail plate. Less commonly, the pigmentation can involve the whole nail plate (total melanonychia) or present as a transverse band (transverse melanonychia). Total melanonychia and transverse melanonychia are much rarer occurrences. From a histologic point of view, LM may result either from simple activation of nail matrix melanocytes, benign (lentigo or nevus), or malignant (melanoma) melanocyte hyperplasia.

Melanonychia Caused by Melanocyte Activation

Melanonychia caused by melanocyte activation often involves several nails and is a more common occurrence in those patients with darker skin phototypes. Among African-American patients, "racial" melanonychia affects up to 77% of young adults and almost 100% of those older than 50 years of age; in the Japanese, LM affects 10% to 20% of adults. Nail matrix melanocytes are usually quiescent but possess the enzymes necessary for melanin production and may be activated by different local or systemic causes.^{1,2} Causes of nail matrix melanocyte activation include drugs; inflammatory,

traumatic, mycotic, and neoplastic nail disorders; and systemic diseases.³

Drug-Induced Melanonychia

Drug-induced melanonychia usually involves several nails with multiple light brown to black longitudinal or transverse bands. The vast majority of transverse melanonychia belongs to this category. Chemotherapeutic agents, especially when administered as multiple drugs, are the principal cause of drug-induced melanonychia.⁴ Other drugs that have been implicated include antiretrovirals (lamivudine, zidovudine), antimalarials (mepacrine, amodiaquine, chloroquine), metals (arsenic, thallium, mercury, gold salts), psoralens with UVA, and radiotherapy. The pigmentation usually partially or completely fades after cessation of the drug; however, this fading can take years.

Postinflammatory Melanonychia

Melanocytes can be activated by inflammatory skin diseases that affect the nail unit, such as psoriasis, Hallopeau's acrodermatitis, lichen planus and chronic paronychia. Melanonychia is common in the fingernails of nail biters (onychotillomania) (Fig. 1) and in the toenails exposed to chronic friction from shoes (Fig. 2).

In onychotillomania, trauma to the nail matrix is caused by biting, picking, or chewing the cuticles or by the use of sharp instruments to cut or pull out the nail plate. Activation of nail matrix melanocytes results in bands of diffuse melanin pigmentation, which typically is associated with signs of nail trauma (Fig. 1). These include Beau's lines, onychorrhexis, nail thinning, longitudinal striations, and splitting of the distal margin. Frictional longitudinal melanonychia involves the fifth and/or the fourth toenails, often symmetrically, and results from chronic friction or pressure by the narrow tip of the shoe on the proximal nail fold overlying the bony phalanges. LM may involve a part of or the whole nail plate, is usually brown in color, and is not associated with nail plate abnor-

*Department of Dermatology, University of Bologna, Bologna, Italy.

[†]Department of Dermatology, Santa Casa de Sao Paulo Hospital, Sao Paulo, Brazil.

Address correspondence to Antonella Tosti, Department of Dermatology, University of Bologna, Bologna, Italy. Correspondence: Antonella Tosti Via Massarenti, 1, Bologna, Italy 40138. E-mail: antonella.tosti@unibo.it



Figure 1 Melanonychia of the fingernails caused by onychotillomania.

malities (Fig. 2). Nail melanocyte activation occurs with trauma of the proximal nail fold overlying the matrix and not with trauma affecting the tip of the toes, as occurs in athletes.

Onychomycosis

In onychomycosis, melanonychia may be caused by melanocyte activation but also by direct melanin production by the fungi. Some nondermatophytic molds (*Scytalidium dimidiatum* and *Alternaria alternata*) and *Trichophyton rubrum* (var *nigricans*) produce pigmented hyphae (dematiaceous) that can cause diffuse or banded nail pigmentation.^{5,6}

Systemic Causes

Although frequently mentioned in textbooks, melanonychia caused by systemic diseases is rare, the most common association being with endocrine disorders, such as Addison's disease.

Benign Conditions

Nonmelanocytic benign and malignant tumors and benign conditions often cause melanonychia by stimulation of melanocytes; these include onychomatricoma, Bowen's disease, squamous cell carcinoma, myxoid cysts, and warts.

Melanonychia Caused by Melanocyte Hyperplasia

The pathology is characterized by a proliferation of melanocytes within the nail matrix and/or the nail bed epithelium. This type of melanonychia is a challenge both for the clinicians and the pathologists to rule out melanoma of the matrix.

Lentigo/Benign Melanocytic Hyperplasia

The prevalence of melanonychia caused by lentigo is not known. The pathological criteria for this diagnosis are not well established, and some authors consider melanocytic hyperplasia to be a potentially malignant lesion.⁷ Lentigo is characterized by an increased number of melanocytes arranged as single cells within the epithelium of the nail matrix.^{8,9} Amin et al¹⁰ found that the number of melanocytes in lentigo ranged from 5 to 31 (with a median 14) per millimeter of basal membrane length.

Benign melanocytic hyperplasia was diagnosed in 12% of the

biopsies of melanonychia in adults¹¹ and 30% in children.⁸ There are no clinical or dermoscopic parameters that allow specific differentiation of melanonychia due to lentigo. The dermoscopic literature does not address this variety of melanonychia but rather places lentigo among the causes of melanocyte activation.¹²

Nevus of the Nail Matrix

Nail matrix nevi typically are seen in young people and may be congenital or acquired. They have been reported to represent approximately 12% of longitudinal melanonychia in adults¹¹ and 48% in children.⁸ The nail has one or more longitudinal pigmented bands varying in size from a few millimeters to the whole nail width and in color from light brown to black.

Dark bands often are associated with pseudo-Hutchinson's sign, because the dark nail plate pigmentation is visible through the transparent nail fold (Fig. 3a, b). The pigmentation may be homogeneously distributed or darker bands may appear over a diffuse pale pigmentation. The fingernails are more often involved than the toenails, with no predilection for a particular digit.

Some clinical features of nail matrix nevi in children can be alarming, including the following:

- Hutchinson's sign, periungual pigmentation: Congenital nevi often involve the nail folds and the hyponychium.
- Variation in the width of the band: In children, it is not uncommon to notice a gradual enlargement of the band that may have a broader proximal part than the distal part, resulting in a triangular shape.
- Variation in the color of the band: Darkening and spreading of the pigmentation is not unusual.

Thinning and fissuring of the pigmented nail plate may also occur.

In children, it is also quite common to observe gradual fading of the band. Fading of the pigmentation is not an indication of regression of the nevus but just of reduced melanin production from nevus cells.¹³ Pathologically, most of the nevi in children are junctional nevi.⁸ The rate of progression of nail matrix nevi to melanoma is not known but is probably rare.

Melanoma

Melanoma of the nail unit is a rare entity, comprising only 0.7% to 3.5% of all forms of melanoma and typically presenting in a more advanced



Figure 2 Longitudinal melanonychia of the fifth toenail caused by chronic friction from shoes.

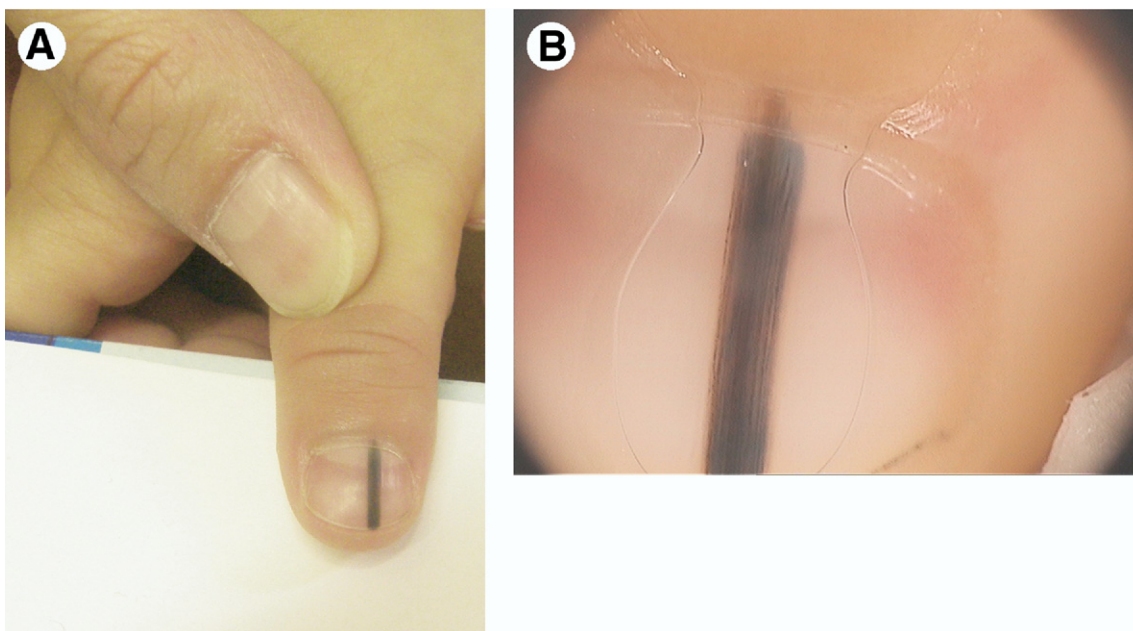


Figure 3 (a) Three-years old boy with a dark band of melanonychia of the right thumbnail. (b) Dermoscopy shows a brown band with longitudinal parallel lines; note the pseudo Hutchinson's sign. The band was excised and pathology revealed a nevus (Fotofinder, $\times 20$ magnification).

stage than other melanomas.¹⁴⁻¹⁶ The overall prognosis is poor, with the 5 year survival rate ranging from 16% to 87% depending on the case series. Delay in the diagnosis is common and is associated with poor prognosis.

Melanoma of the nail bed and matrix is more frequent in ethnic populations. Because most articles on the epidemiology and treatment of melanoma of the nail unit do not distinguish nail matrix melanoma from subungual melanoma but just use the term subungual melanomas to refer to all lesions, we don't really know if most melanomas arise from the matrix or from the nail bed; therefore, we use the term melanoma of the nail unit in the following discussion. Although melanoma of the nail unit represents 1% to 2% of all melanomas in Caucasian populations, it has a prevalence of 10% to 23% in Asian populations and 25% in African-American populations.^{3,17} Melanoma of the nail unit may occur at any age, but it is a rare occurrence in children.¹⁸ There is no demonstrable association between the development of subungual melanoma and melanoma of the nail matrix with excessive exposure to ultraviolet light. The nail plate acts as a barrier to UVB radiation. Although trauma is often implicated as the putative factor, its role as the causative factor is unknown.¹⁹

The thumb and the big toe are the most frequently affected locations. In a study performed by Tan and colleagues¹⁴ in which they examined 124 cases of melanoma of the nail unit (the largest series reported until now), the most common site was the great toe (24%) followed by the thumb (18%). A study performed by Cohen and colleagues¹⁶ of 49 patients showed that most patients were female with a median age of 66 years; the most common site again was the big toe (53%), followed by the thumb (31%) and the fifth finger (10%).

The clinical presentation of melanoma of the nail unit depends on the site of origin which is either the nail matrix or the nail bed. The appearance is summarized as follows:

Nail Matrix Melanoma

Lesions that originate in the nail matrix usually cause a banded pigmentation of the nail plate (longitudinal melanonychia). This is

the first symptom in up to 70% of cases. The color of the band is usually light brown to black and of variable width (Fig. 4a, b). The nail plate may present as fissure or a split corresponding to the band, indicating compression or destruction of the nail matrix epithelium by the melanoma.

Nail Bed Melanoma (Subungual Melanoma)

This causes a pigmented or nonpigmented (25% to 30% of cases) subungual nodule. Nail bed ulceration and bleeding occur when the tumor grows. Clinical differential diagnosis with ulcerated nail bed tumors and with nail bed pyogenic granuloma is often impossible.

An ABCDEF rule for the early detection of melanoma of the nail unit has been proposed (Table 1).²⁰ Hutchinson's sign describes the presence of pigmentation in the periungual skin and represents the radial growth phase of melanoma of the nail unit. Although Hutchinson's sign is not exclusive to melanoma, its presence requires a biopsy (Table 2).

Dermoscopy

When performed by trained examiners, dermoscopy has already proven its efficiency in the differential diagnosis of cutaneous pigmented tumors. The main difficulty in the evaluation of nail pigmentation is that the lesions that are examined with dermoscopy correspond to melanin deposition in the nail plate and not to the site of melanin production, which is in the nail matrix or in the nail bed. Intraoperative nail matrix dermoscopy permits more accurate diagnosis but it is an invasive procedure that cannot be used routinely.

Dermoscopy also has been proposed before surgery to select the anatomic site to be explored. Examination of the distal edge of the nail establishes the localization of pigment within the nail plate and then which part of the matrix is involved. Pigmentation of the lower nail plate corresponds to a distal nail matrix origin, and pigmentation of the higher nail plate corresponds to a proximal localization of responsible melanocytes. In most cases of melanonychia, the pig-

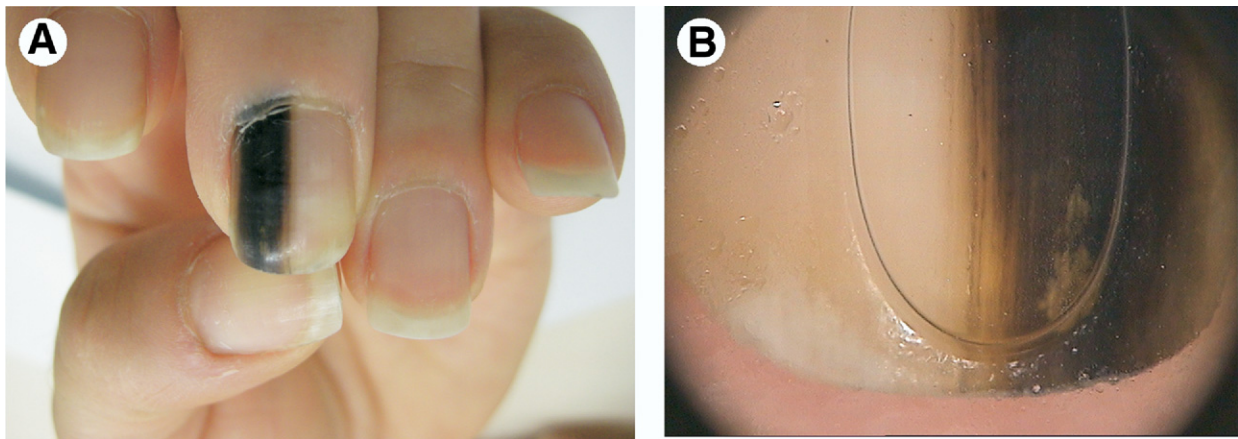


Figure 4 (a) Longitudinal melanonychia due to melanoma of the nail matrix. (b) Dermoscopy shows a brown band with longitudinal lines with irregular coloration, spacing and thickness and parallelism disruption (Fotofinder, $\times 20$ magnification).

ment is in the lower (ventral) part of the nail plate as most bands originate from the distal matrix.²¹

Nail Plate Dermoscopy

Dermoscopy of the nail plate always requires oil or gel immersion because of the convex shape of the nail. Dermoscopic patterns for evaluation of nail pigmentation have been described but their accuracy in the diagnosis of subungual melanoma has not been established.^{12,22-24} Similarly, there are no evidence-based studies to inform the clinician as to the frequency of dermoscopic follow-up in patients with melanonychia. There are no precise dermoscopic criteria that can be used to decide when to biopsy the lesion. Dermoscopy of the nail plate permits differential diagnosis between non-melanocytic and melanocytic pigmentation and may permit differential diagnosis between nail matrix melanocyte activation and hyperplasia but should not be considered a substitute for pathology in the differential diagnosis of longitudinal melanonychia.

Dermoscopic Patterns That Suggest Subungual Hematoma

Irregularly-shaped purple to brown-black areas with round, dark red spots at the periphery and a “filamentous” distal end are patterns that have been associated with subungual hematomas. However, we should remember that the presence of blood extravasation does not exclude an associated melanoma.

Table 1 ABCDEF Mnemonic for Subungual Melanoma

A	age (peak in 5th-7th decades), Asian, African-Americans, Native Americans
B	brown to black band width breadth of 3 mm or more with variegated borders
C	change in nail band despite treatment
D	digit
E	extension of pigment onto the proximal and/or lateral nailfold (Hutchinson’s sign)
F	family or personal history of dysplastic nevus or melanoma

Dermoscopic Patterns That Suggest a Diagnosis of Melanocyte Activation

A gray background with thin gray regular parallel lines suggests melanonychia due to nail matrix melanocyte activation. In traumatic melanocyte activation, tiny dark red to brown spots corresponding to blood extravasation may also be seen.

Dermoscopic Patterns That Suggest a Diagnosis of Nevus

The presence of a brown background with longitudinal brown to black regular parallel lines often suggests a nevus. In children, black dots (less than 0.1 mm) similar to those described in skin melanocytic lesions are frequently observed and correspond to pigment accumulation in the nail plate.

Dermoscopic Patterns That Suggest a Diagnosis of Melanoma

Brown background with longitudinal, brown to black lines with irregular coloration, spacing or thickness and parallelism disruption suggest melanoma. Dermoscopy also can be used to detect Hutchinson’s sign before clinical detection by unaided visual inspection. Dermoscopy of eroded nodules of the nail bed often permits detection of peripheral pigmentation in amelanotic melanoma, allowing differential diagnosis from pyogenic granuloma and non-melanocytic nail tumors.

Nail Matrix Dermoscopy

Intraoperative dermoscopy permits direct visualization of the site of melanin production in the nail bed or matrix with patterns that are

Table 2 Nail Pigmentation: Clinical Signs that Suggest Immediate Excisional Biopsy of the Pigmentation to Exclude Nail Melanoma

- Lack of homogeneity of the pigmentation, with bands or lines of different color
- Presence of nail plate fissuring or splitting
- Proximal part of the band broader than the distal (triangular shape)
- Blurred lateral borders of the band
- Pigmentation of the periungual skin (Hutchinson’s sign)

similar to those found in skin melanocytic lesions. Dermoscopy of the nail bed and matrix is also very useful to select the surgical margins, and may avoid omission of small pigment foci.^{25,26}

Management

The main challenges in the management of a patient with melanonychia are to distinguish melanoma from benign conditions (avoiding delayed diagnosis), to define proper guidelines for follow-up, to establish the best modality for obtaining a pathological sample from a suspicious lesion, and to establish the pathological diagnosis of in situ melanoma.

Early Diagnosis of Subungual Melanoma and Melanoma of the Nail Matrix

Early diagnosis and treatment of melanoma offer the only possibility of curative treatment. When considering a pigment band, we should first establish whether the pigmentation is caused by melanin or by another pigment. If the pigmentation is melanin, then it is important to differentiate bands caused by melanocyte activation from bands caused by melanocyte hyperplasia. This can usually be done by history, clinical examination, and dermoscopy.

Nonmelanin nail pigmentation and melanonychia caused by melanocyte activation do not need invasive investigations and close follow-up. Management depends on the patient's age. We believe that it is probably advisable to obtain a biopsy for bands caused by melanocytic hyperplasia in adults but not in children, in whom a "wait-and-see" attitude can be adopted until puberty. However, the decision must also take into account the size of the lesion, because small (3 mm) bands can be excised without residual scarring. Excision avoids anxiety of patients and parents who may be reluctant to accept "simple" clinical follow-up. It is always important to ask for personal or familiar history of melanoma or atypical nevi syndrome.

In adults, clinical features that suggest melanoma and require immediate excision and pathological study of the pigmented band include a single affected digit, lack of homogeneity with bands or lines of different color, presence of nail plate fissuring or splitting, rapid enlargement of the band, a proximal part of the band that is broader than the distal part (triangular shape), blurred lateral borders of the band, and pigmentation of the periungual skin.

Follow-Up of Pigmented Bands

There is no consensus on modalities for follow-up of pigmented bands in adults and children. Prospective studies are needed as evidence-based information is lacking. In general, bands with alarming clinical or dermoscopic features should be completely excised. Although melanoma is reported to be rare in children, one of us (AT) has personally diagnosed three cases of in situ nail matrix melanoma in children in the last three years, including a published case¹⁸ in an Hispanic girl and two unpublished cases in fair-skinned Caucasian children. Follow-up requires periodic medical examinations/visits, photographic and dermoscopic documentation.

Biopsy Versus Excision

In bands with suspicious clinical and/or dermoscopic features, the definitive diagnosis can only be made histologically. Although most of the literature on the pathology of melanonychia is based on data obtained with incisional biopsies, mainly punch biopsies, there is evidence that these may produce false-negative results because the pathological examination will not evaluate the whole lesion. Several cases of delay in treatment of melanoma of the nail unit caused by

false-negative incisional biopsies are reported in the literature.^{7,18,27} An excisional biopsy is recommended for a definitive diagnosis based on pathological evaluation of the whole lesion.

The shave biopsy of the nail matrix (also referred to as a tangential matrix excision)²⁸ is an alternative to either single or multiple 3-mm punch biopsies, larger punch biopsies, or transversely oriented excisional biopsies, as it can obtain an optimal pathological sample with minimal scarring.²⁹

Pathological Diagnosis

Differential diagnosis between benign melanocytic hyperplasia and in situ melanoma can be a serious problem for the pathologist. Amin et al¹⁰ evaluated the density and the characteristics of intraepidermal melanocytes in pathological specimens of benign lentigo and in situ and invasive melanoma. An increase in the density of intraepidermal melanocytes was one of the earliest histologically alterations associated with in situ melanoma. In Caucasian patients, the mean melanocyte density in the nail matrix is of 6.5 cells per millimeter of basal membrane length. Variations may be related to anatomical site because melanocytes tend to be more numerous in the distal than in the proximal portion of the nail matrix. The mean melanocyte density in specimens of in situ melanoma was approximately 4 times greater than the mean melanocyte density of lentigo.¹⁰ Although the authors were not able to establish a cut-off value in the melanocytic density to separate in situ melanoma from benign lentigo, Amin et al¹⁰ concluded that a low melanocytes density strongly favors a benign process, whereas a melanocytic density of 40 or greater favors a diagnosis of in situ melanoma.

Other relevant pathological features that can be helpful for differential diagnosis between lentigo and in situ melanoma include:

- confluency of cells, described as a focal row of melanocytes directly apposed to each other: this feature was seen in melanoma, but not in benign lentigo;
- multinucleation and inflammation, are not found in benign lentigo and nevi, but rather they are seen in melanoma;
- florid pagetoid cell spreading, not found in benign lentigo and diagnostic for *in situ* melanoma.
- severe atypia, which was only seen in melanoma, but was uncommon.

Conclusions

Dealing with melanonychia is still a challenge for clinicians with many unanswered questions. In the absence of consensus recommendations from a panel of experts, after reviewing evidence-based publications, we offer our recommendations about 2 common clinical problems.

First Problem

Melanonychia in children: is the wait and see policy acceptable?

Information about the prevalence of nail matrix nevi in children is completely lacking. There are different opinions on whether a single band of LM with clinical and dermoscopic features suggesting melanocyte hyperplasia should be excised or not. If it should be excised, then when it is appropriate to do so, (for example, at the time of diagnosis, when the lesion is clinically stable, or after puberty), is unknown.

Prospective studies are needed to see whether dermoscopy is useful to select lesions that should be immediately excised from lesions that can be followed. Also, the interval of follow up needs to be determined. An excisional shave biopsy is possibly the best tech-

nique to evaluate the whole lesion and provide accurate diagnosis without leaving a definitive nail dystrophy. This approach is still new and requires confirmation.

We have no data at all about progression of nevi that have not been excised. There is evidence that some nevi may become “amelanotic;” therefore, they are clinically invisible and possibly persist undetected in adult life. The significance of benign melanocytic hyperplasia is unknown as is the possible risk of evolution to malignant melanoma.

Our attitude is to excise, with a nail matrix shave biopsy, lesions with alarming clinical and/or dermoscopic features, particularly bands that enlarge or darken, and to follow up every 6 months all the other lesions that we usually excise after puberty.

Second Problem

Is Nail Plate Dermoscopy Reliable in the Evaluation of Nail Pigmentation?

The experience in this field is still limited, and there are no data showing that dermoscopy is superior to clinical evaluation in early detection of melanoma of the nail unit. In 2007, Professor Nilton Di Chiacchio from San Paulo and one of the authors (AT) founded an International Study Group on Melanonychia, which now has 30 members from 12 countries around the world with the goal of defining the fields that need investigation and of providing evidence-based information to clinicians dealing with nail pigmentation. These include creation of a melanonychia registry on a dedicated Web site, pathological consensus on diagnosis of pigmented nail lesions, consensus on guidelines for management of melanonychia in children, follow-up of patients undergoing excisional biopsies with different techniques to establish recurrence rate, long-term follow-up of nevi with nail plate dermoscopy. This will possibly permit collection of evidence based data to diagnose and manage patients with melanonychia better and then improve the prognosis of patients with subungual melanoma.

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