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INVITED ARTICLE

# Key points in dermoscopic differentiation between early acral melanoma and acral nevus

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## ABSTRACT

Acral skin is the most prevalent site of malignant melanoma in non-Caucasian populations. On acral skin, other various kinds of pigmented lesions are also detected. Particularly, melanocytic nevus is commonly seen on acral volar skin; approximately 10% of Japanese have a nevus on their soles. Prognosis of acral melanoma is still generally poor because of delayed detection in the advanced stages. To improve the prognosis, early detection is essential. Early acral melanoma is seen as a brownish macule, which is clinically quite similar to acral nevus. Therefore, clinicians often face a dilemma when they see a pigmented macule on acral volar skin. Introduction of dermoscopy was a great epoch in this field. Pigmentation pattern on dermoscopy is completely opposite between early acral melanoma and acral nevus; pigmentation on the ridges of the surface skin markings is detected in early acral melanoma, whereas pigmentation along the furrows of the skin markings is seen in acral nevus. We termed these dermoscopic patterns the parallel ridge pattern and the parallel furrow pattern, respectively. These features are highly helpful in the differentiation between the two biologically distinct entities. The sensitivity and specificity of the parallel ridge pattern in diagnosing early acral melanoma is 86% and 99%, respectively. However, we must be aware that dermoscopic features in acral nevus sometimes mimic the parallel ridge pattern and that other conditions also could show dermoscopic features similar to the parallel ridge pattern. In this review article, we summarize key points of the dermoscopic diagnosis of early acral melanoma and then describe the three-step algorithm for the management of acral melanocytic lesions, which surely aids us in effectively detecting early acral melanoma and in reducing unnecessary resection of benign nevus.

**Key words:** acral melanoma, acral nevus, dermoscopy, early detection, three-step algorithm.

## INTRODUCTION

Malignant melanomas affecting acral skin are called acral lentiginous melanoma according to Clark's classification.[1] Clark's classification was criticized by Ackerman, who insisted on the unifying concept of malignant melanoma.[2] Bastian's group recently proposed a new classification of melanoma, in which acral melanoma was defined as melanomas affecting the palms, soles and nail apparatus.[3] Acral lentiginous melanoma of Clark's classification is not identical to acral melanoma of Bastian's classification because five out of 36 acral melanomas in Bastian's original series were diagnosed as superficial spreading melanoma according to Clark's criteria.[3] It is important that acral melanoma of Bastian's classification has unique molecular and genetic characteristics distinct from other types; frequent amplifications or mutations of the cyclin D1 (11q13), the cyclin-dependent kinase (*CDK*)*4* (12q14), the human telomerase reverse transcriptase (*hTERT*) (5p22) and the *KIT* (4q12) genes are among them.[4]

Acral melanoma is the most prevalent type of malignant melanoma in non-Caucasian populations.

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In Japanese, acral melanoma accounts for approximately 50% of all melanomas,[5] and the rate is almost the same among other Asians including Chinese and Korean. The proportion of acral melanoma is much higher in black persons. Although the proportion of acral melanoma is very low in Caucasians, absolute incidences of acral melanoma seem to be almost the same among all races including Caucasians.[4] The low proportion of acral melanoma in Caucasians is due to an extremely high incidence of the superficial spreading melanoma of Clark's classification, which is mostly identical to melanoma affecting the non-chronically sun-induced damaged skin of Bastian's classification. Prognosis of acral melanoma is generally poor primarily due to delayed detection in the advanced stages.[6] Therefore, accurate diagnosis and adequate treatment of acral melanoma in early curable stages are essentially important to improve the prognosis.

## CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF EARLY ACRAL MELANOMA

Melanocytic nevi are commonly seen on acral volar skin. According to a recent study, approximately 10% of Japanese have melanocytic nevus on the sole.[7] Most acquired acral nevi are histopathologically junctional or compound types with a predominant junctional component, and thus clinically observed as a brownish black macule. Early acral melanoma is also clinically recognized as a brownish black macule. Thus, clinicians feel a dilemma when they see a pigmented macule on acral volar skin; whether it is a benign nevus or an early melanoma. By early 1990s, one of the authors (T. S.) described clinical and histopathological characteristics of early acral melanoma.[8] The proposed clinical criteria for early acral melanoma were as follows: (i) a pigmented macule with variable shades of brown from tan to black; (ii) irregular and asymmetric shape often accompanied by notching at the periphery; and (iii) a large lesion mostly more than 7 mm in maximum diameter. However, sensitivity and specificity of the criteria are not satisfactory; not a few acral nevi fulfill these criteria and evolving small early acral melanoma is overlooked with the criteria.

The histopathological criteria we proposed for the diagnosis of early acral melanoma were as follows: (i) a broad lesion of more than 7 mm in width; (ii) asymmetrical and irregular overall histopathological configuration; (iii) solitary arranged melanocytes in the epidermis detected at least focally, often reaching to the upper epidermis; and (iv) poorly demarcated nests of melanocytes of variable size and shape, showing a tendency to coalesce.

In contrast, most acquired acral nevi are clinically recognized as an evenly pigmented brownish black macule, oval or spindle in shape and usually well demarcated. The size is small, mostly 7 mm or less in maximum diameter, though congenital nevus could be large. Histopathologically, acral nevus shows almost symmetrical overall configuration. Melanocytes (nevus cells) are arranged mostly in well-demarcated nests mainly located at the dermo-epidermal junction. However, in acral nevus, solitary arranged melanocytes are not infrequently detected in the lower epidermis and occasionally even in the upper epidermis. It was reported that random solitary arrangement of melanocytes could be prominent in acral nevus, particularly when the tissue sections are cut parallel to the skin markings.[9] These features cause confusion in histopathological differentiation of acral nevus from early acral melanoma.[10]

Thereafter, our group started dermoscopic investigation of acral lesions and found dermoscopy was immensely helpful in the differentiation between early acral melanoma and acral nevus.[10–15] Moreover, these dermoscopic findings led us to propose new criteria for histopathological diagnosis of very early acral melanoma that is difficult to diagnose with the conventional histopathological criteria.[16] In an early evolving lesion of acral melanoma, solitary arranged melanocytes preferentially proliferate in the crista profunda intermedia, an epidermal rete ridge underlying the surface ridge. This finding is well recognized in the tissue section cut perpendicularly to the surface skin markings. In contrast, in acral nevus, melanocytes (nevus cells) are mostly arranged in well-demarcated nests mainly located in the crista profunda limitans underlying the surface furrow. More recently, however, we have found nests of nevus cells are not always limited to the crista profunda limitans but could be detected also in the crista profunda intermedia. Very interestingly, even in such a case,

melanin columns in the cornified layer are derived from the nests in the crista profunda limitans and not from those in the crista profunda intermedia.[17] In contrast, in an early evolving lesion of acral melanoma, melanin granules in the cornified layer are mainly derived from increased melanocytes in the crista profunda intermedia and are mostly detected under the ridges of the skin markings. In our view, these subtle but very significant histopathological findings are very helpful in the histopathological differentiation between early acral melanoma and benign acral nevus.[17]

## DERMOSCOPIC FEATURES OF ACRAL NEVUS

There are three major dermoscopic patterns in acral nevus: the parallel furrow, lattice-like and fibrillar patterns (Fig. 1).[11–14] More than 75% of acral nevi exhibit one of these three major patterns. The parallel

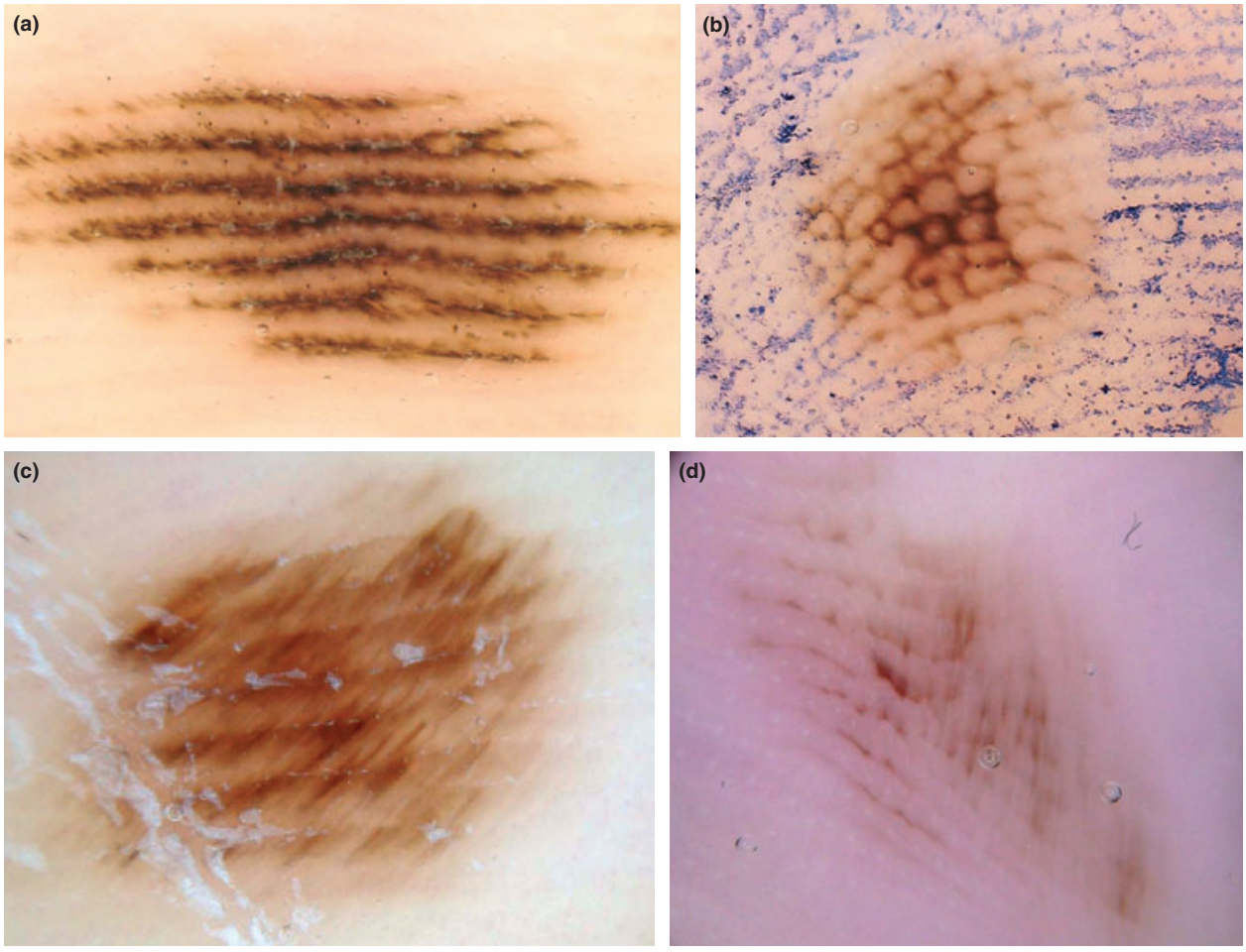


**Figure 1.** Major dermoscopic patterns of acquired acral nevus. (a) The parallel furrow pattern, in which parallel pigmented lines are seen along the furrows of the skin markings. (b) The lattice-like pattern, composed of the parallel lines on the furrows as well as of the lines bridging the parallel lines, resulting in a lattice-like pigmentation. Peripheral blue pigmentation seen in the furrows of this photograph is ink of a whiteboard marker pen used for the furrow ink test (see the text and Fig. 5). (c) The fibrillar pattern formed by densely packed fine fibrillar pigmentation arranged in the direction crossing the parallel skin markings. Note that endpoints of the fibrils composing this regular fibrillar pattern are lined up on the straight lines corresponding to the surface furrows. (d) In this acral nevus, the parallel furrow pattern is seen on the left lower side and the fibrillar pattern on the right upper side. This is an expected finding because the fibrillar pattern is a modification of the parallel furrow pattern.

 

furrow pattern is most prevalent among the three patterns, accounting for approximately 45–50% of all acral nevi, followed by the lattice-like pattern (15–25%), and then by the fibrillar pattern (10–20%).[18] The parallel furrow pattern shows brownish linear pigmentation along the sulci of the surface skin markings, namely, dermatoglyphic grooves (Fig. 1a). There are several subtypes of the parallel furrow pattern, such as dotted-line and double-line subtypes.[13] Among these, the basic type of the parallel furrow pattern is composed of single solid lines on the sulci. The lattice-like pattern consists of parallel lines along the sulci as well as lines bridging the parallel lines (Fig. 1b). The fibrillar pattern shows densely packed, fibrillar pigmentation, usually arranged in the direction crossing the skin markings (Fig. 1c).

Studies by our group have revealed that the parallel furrow pattern is the prototype of the three major dermoscopic patterns in acral nevus.[18] Histopathologically, the parallel furrow pattern is caused by melanin columns in the cornified layer derived from nests located in the crista profunda limitans situated under the surface furrow. Acral nevi of the lattice-like pattern are mainly found in the arch areas on the sole or at peripheral portions of the palm and sole, where the skin markings show a crisscross pattern, reflecting the well-developed transverse ridges bridging the crista profunda limitans and the crista profunda intermedia in these areas. Pigmentation in the lattice-like pattern is seen along the sulci of these crisscross skin markings.[15] Thus, this pattern is essentially common to the parallel furrow pattern in that the pigmentation is seen along the sulci. In this sense, the lattice-like pattern can be regarded as an anatomical variant of the parallel furrow pattern.[18] In addition, we have found that the fibrillar pattern is caused by an oblique arrangement of melanin pigment distributed in the slanting cornified layer induced by mechanical pressure from the bodyweight.[15] Even in the fibrillar pattern, melanin granules in the cornified layer are derived from the nests of nevus cells located in the crista profunda limitans, as they are in the parallel furrow pattern. Therefore, the fibrillar pattern can be regarded as an artifactual expression of the parallel furrow pattern.[18] These three major dermoscopic patterns occasionally coexist in a single acral nevus (Fig. 1d). This is an expected finding because all these patterns are variants of the parallel furrow pattern as described above.

Several other dermoscopic patterns are detected in acral nevus, such as the globular, homogeneous, reticular, transition and globulostreak-like patterns.[19–22]

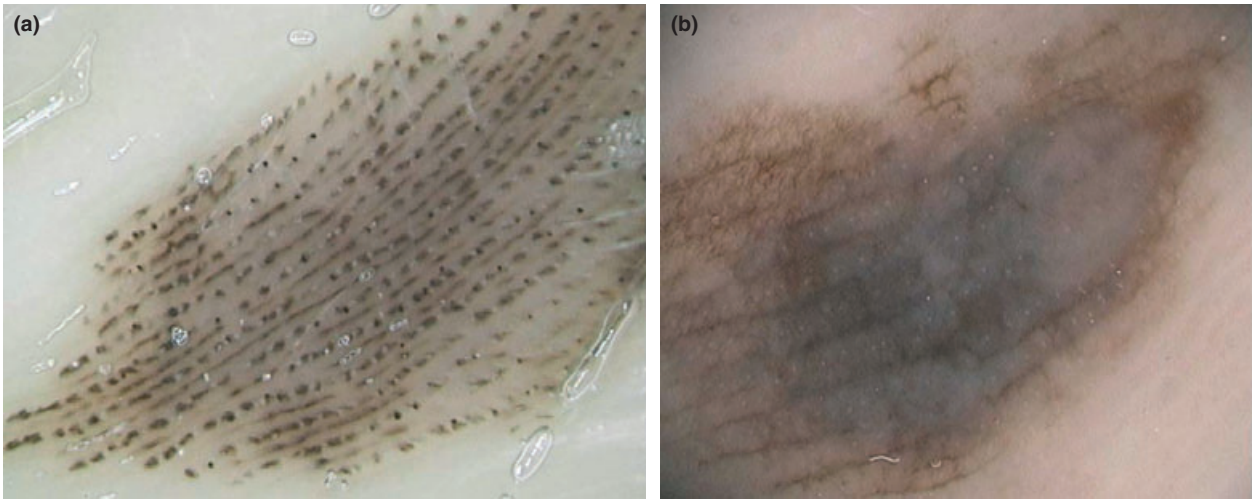


**Figure 2.** Dermoscopic features of congenital acral nevus. (a) In addition to the parallel furrow pattern, brown globules are regularly distributed on the ridges of the skin markings. We call this feature the peas in a pod pattern. The globules reflect nests of nevus cells surrounding the distal portions of eccrine ducts, an expected feature in congenital nevus, in which adnexocentricity of nevus cells is a common histopathological feature. (b) In this congenital acral nevus, in addition to the parallel furrow or the lattice-like pattern, a broad, bluish-gray, structureless area is detected. The bluish-gray area suggests a prominent intradermal component in this nevus, which is also an expected histopathological feature of congenital nevus.

In our estimation, all these are minor patterns detected in less than 5% of acral nevi. In our previous papers, we lumped together all these minor dermoscopic patterns not conforming to any of the three major patterns under the term non-typical pattern.[11,13]

In addition, we recently described characteristic dermoscopic patterns seen in congenital acral nevus such as the peas in a pod pattern (Fig. 2a).[23] Rather structureless bluish-gray pigmentation also could be detected on dermoscopy in congenital acral nevus with a predominant intradermal component (Fig. 2b).

## DERMOCOPIC CHARACTERISTICS OF ACRAL MELANOMA

The most important dermoscopic feature detected in primary lesions of acral melanoma is the parallel ridge pattern.[12,14] This pattern is composed of parallel band-like pigmentation on the ridges of the surface skin markings. This is in contrast to the parallel furrow pattern, the prototypical dermoscopic pattern seen in acral nevus, in which parallel linear pigmentation is seen on the furrows of the skin markings.[24] In early acral melanoma, the parallel ridge pattern covers almost the entire lesion and the color of the pigmentation is light brown in most cases (Fig. 3a). However, in the more advanced acral melanoma, the parallel ridge pattern is detected focally within the lesion and the color of the parallel bands is usually more dense, ranging from dark brown to black (Fig. 3b), which reflects a large amount of melanin granules produced by melanocytes in the epidermis. The sensitivity and specificity of the parallel ridge pattern are 86% and 99%, respectively, not only in the advanced acral melanoma but also in acral melanoma *in situ*.[14] These data clearly indicate that the parallel ridge pattern is highly helpful in detecting early acral melanoma. Corresponding to the parallel ridge pattern, histopathologically, melanocytes of early acral melanoma preferentially proliferate in the crista profunda intermedia, an epidermal rete ridge situated under the surface ridge.

Another dermoscopic pattern seen in acral melanoma is irregular diffuse pigmentation, showing rather structureless, diffuse, brownish-black pigmentation with variable shades, occasionally also associated with grayish tone (Fig. 4a).[12,14] This finding reflects histopathological features of diffuse proliferation of melanocytes within the epidermis, and sometimes even in the upper dermis. Therefore, the irregular diffuse pigmentation is observed in more advanced lesions of acral melanoma compared with the parallel ridge pattern.[13,14] Sensitivity and specificity of the irregular diffuse pigmentation are 69% and 97% in acral melamoma *in situ* and 94% and 97% in invasive

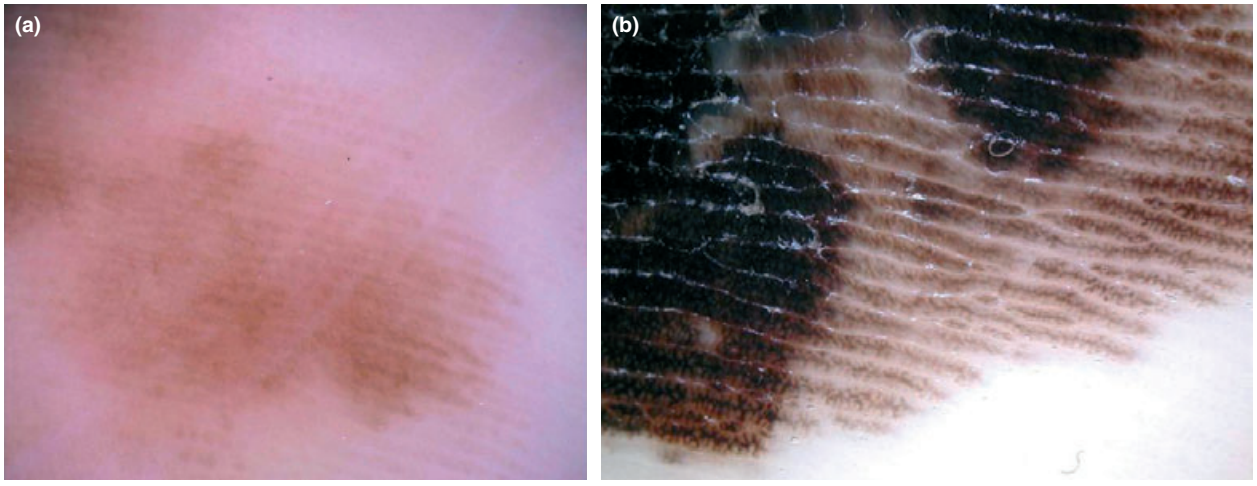


**Figure 3.** The parallel ridge pattern, a unique dermoscopic pattern seen in acral melanoma. (a) In this early acral melanoma *in situ*, light-brown, band-like pigmentation is seen on the ridges of the skin markings. (b) In this rather progressed acral melanoma, the color of the parallel ridge pattern is much darker; brownish black or black. The degrees of darkness of the brown color are determined by the amount of melanin granules in the epidermis, which mostly reflects the degrees of proliferation of melanocytes in the crista profunda intermedia.

 

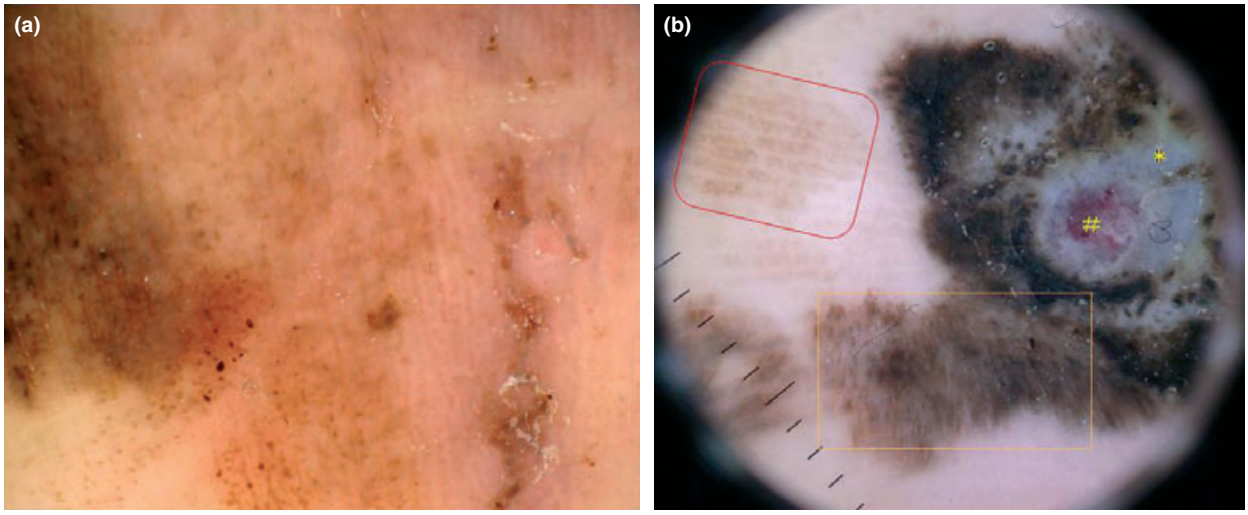


**Figure 4.** Dermoscopic features of acral melanoma in advanced stages. (a) The main feature is irregular diffuse pigmentation with variable shades. Irregular dots/globules and a subtle sign of the irregular parallel furrow pattern are also detected in this case. (b) In this far-advanced acral melanoma, blue white veil (*) and ulceration (#) are detected along with the irregular fibrillar pattern (yellow square). Note that in the peripheral macular areas of the lesion, the light-brown parallel ridge pattern is detected (red square).

melanoma, respectively.[14] Higher sensitivity of the irregular diffuse pigmentation in invasive melanoma compared with melanoma *in situ* is expected because this dermoscopic finding reflects more florid proliferation of melanocytes along the epidermis.

In much more advanced lesions of acral melanoma, other dermoscopic features seen in advanced melanoma on other anatomical sites are detected, such as irregular dots/globules, irregular streaks, blue-white veil, ulceration and polymorphous vessels (Fig. 4b). Moreover, the atypical parallel furrow pattern, the atypical lattice-like pattern, and the irregular fibrillar pattern could be focally detected within the lesions of advanced acral melanoma.

## SIGNIFICANCE OF DERMOSCOPIC DIFFERENCES BETWEEN EARLY ACRAL MELANOMA AND ACRAL NEVUS

As described above, early acral melanoma and acral nevus exhibit highly characteristic dermoscopic features, respectively. A unique dermoscopic feature most frequently detected in early acral melanoma is the parallel ridge pattern, while the most prevalent dermoscopic pattern in acral nevus is the parallel furrow pattern and its variants.[13,14] Thus, a pigmentation pattern is completely opposite between early acral melanoma and acral nevus: pigmentation on the ridges in early acral melanoma versus pigmentation along the furrows in acral nevus. This morphological difference is very interesting not only clinically but also basically. It certainly reflects different biological properties of the proliferating melanocytes in the two entities.[24] From these findings, we realize that the sites of proliferation of melanocytes in the epidermis, the regulation of melanin production and transfer of melanin granules to the surrounding keratinocytes are essentially different between early acral melanoma and acral nevus.[17] How can we explain the reasons for the preferential proliferation of transformed melanocytes of early acral melanoma in a particular rete ridge? We hypothesize that the concept of the cancer stem cell could explain the selective proliferation of melanocytes in the crista profunda intermedia.[4] Although precise molecular mechanisms underlying these differences remain to be investigated, these dermoscopic findings are immensely helpful in the differentiation of the two entities and aid us in detecting acral melanoma in early curable stages. Note that the specificity of the parallel ridge pattern in acral melanoma is 99% from the early *in situ* stage. On the other hand, the positive predictive value of the parallel furrow pattern and/or the lattice-like pattern is 98% in acquired acral nevus.[14]

Therefore, a vast majority of the two entities can be definitely diagnosed by evaluating the dermoscopic patterns.

As mentioned above, in early evolving stages of acral melanoma, the parallel ridge pattern is light brown in color and covers almost the entire lesion (Fig. 3a). In more progressed acral melanoma, the band-like pigmentation is usually darker, from dark brown to black (Fig. 3b). Corresponding to the colors of the dermoscopic pattern, in very early acral melanoma, relatively few transformed melanocytes proliferate as solitary units exclusively in the crista profunda intermedia situated under the surface ridge.[16] The degree of the proliferation of melanocytes in the rete ridges becomes higher with progression of the lesion and the parallel ridge pattern becomes denser in color. In much more advanced lesions of acral melanoma, the irregular diffuse pigmentation is the most predominant dermoscopic feature (Fig. 4a). However, even in advanced acral melanoma with disorganized dermoscopic features, in most cases, the parallel ridge pattern could be focally detected in the macular portions within the lesion (Fig. 4b).

## KEY POINTS IN DERMOSCOPIC DIAGNOSIS OF EARLY ACRAL MELANOMA

In dermoscopic evaluation of acral melanocytic lesions, it is crucially important to judge whether the pigmentation is on the surface ridges or along the surface furrows. However, this judgment is not always easy. For this judgment, the furrow ink test, originally proposed by Braun *et al.*[25] and later revised by Uhara *et al.*[26] is very helpful (Fig. 5). The method is easy; first clean the skin surface with a wet paper towel, then mark the peripheral parts of the lesion with the whiteboard marker pen, preferably blue or green in color, and gently wipe the skin surface with a dry paper towel. Then, we can identify the surface furrows clearly stained with the blue or green ink under dermoscopy, by which we can easily judge whether the pigmentation is on the ridges or along the furrows. Thereby, we can determine whether the dermoscopic feature is the parallel ridge pattern or the parallel furrow pattern. After observation, the ink in the furrows can be easily removed by wiping with a wet paper towel.[26]

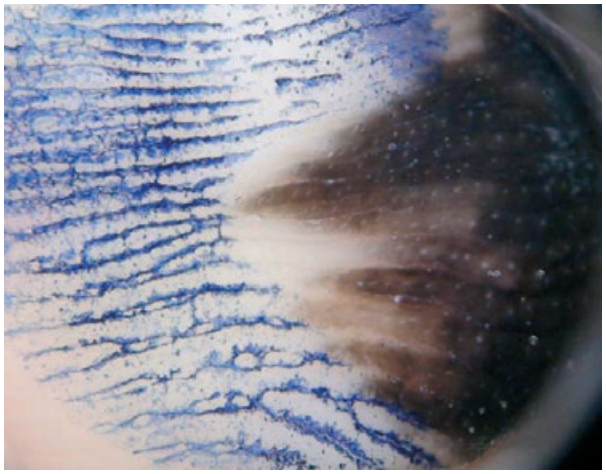

**Figure 5.** The furrow ink test. The furrows of the skin markings are clearly stained with blue ink of the whiteboard marker pen. By this staining, the pigmentation pattern on the right side can be judged as the parallel ridge pattern.

In 1990, our group proposed a guideline of the ''7-mm criterion'', which recommended to biopsy an acral pigmented lesion more than 7 mm in maximum diameter.[27] This was a simple, objective guideline though there were some limitations. Thereafter, we found characteristic dermoscopic features of acral nevus and acral melanoma. Considering the very high specificity of the parallel ridge pattern in early acral melanoma, we recommended to biopsy a pigmented lesion exhibiting the parallel ridge pattern even when it is small, less than 7 mm in diameter.[28] Taking all these findings into consideration, in 2007, we proposed the three-step algorithm for the management of acquired acral melanocytic lesions.[18] More recently, we revised the three-step algorithm in which we introduced a category with no need for further follow up (Fig. 6).[29] The revised three-step algorithm proceeds as follows; in the first step, if a lesion shows the parallel ridge pattern, we biopsy it regardless of the size. If the lesion does not show the parallel ridge pattern, as the second step evaluation, we check whether it shows typical benign dermoscopic patterns (typical parallel-furrow, typical lattice-like or regular fibrillar pattern) or not. If the lesion shows these typical benign patterns, there is no need of further follow up. However, in the second step, if the lesion does not show these typical dermoscopic patterns, we go to the next step. In the third step, we measure the maximum diameter. If the lesion is more than

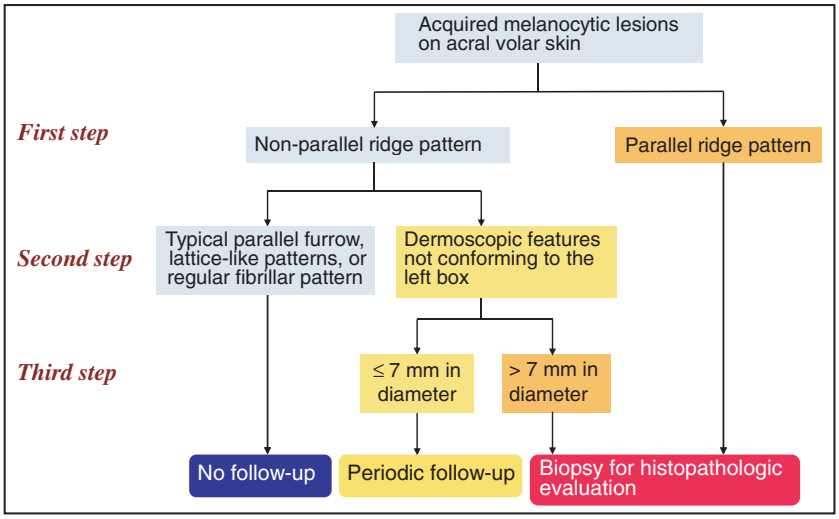


**Figure 6.** The three-step algorithm for the management of acquired acral melanocytic lesions. See the text for details. This figure was modified from reference no. 29.

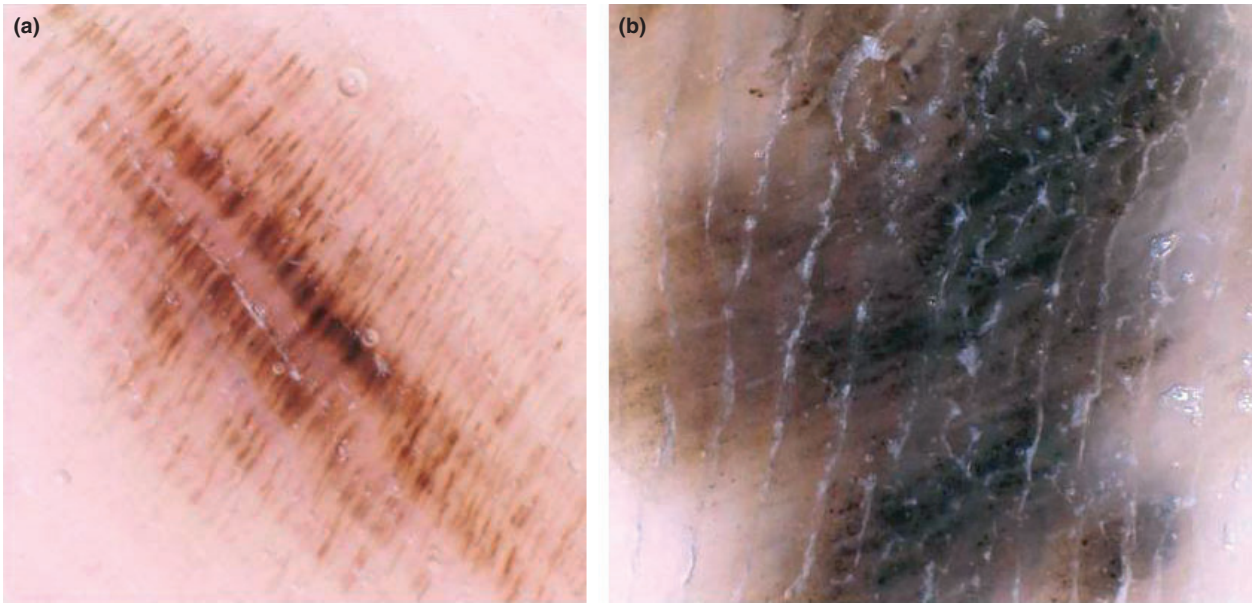


**Figure 7.** Dermoscopic features of the (a) regular and (b) irregular fibrillar patterns. (a) In the regular fibrillar pattern seen in acral nevus, overall dermoscopic features are symmetrical and regular, and end-points of fibrils composing the fibrillar pattern are mostly arranged on straight lines corresponding to the surface furrows. (b) In contrast, in the irregular fibrillar pattern seen in acral melanoma, the fibrils composing the fibrillar pattern are arranged in a disorganized fashion. Thickness and length of the fibrils are random and irregular, and the end-points of the fibrils are not lined up on a straight line.

7 mm in maximum diameter, we recommend to biopsy it, while if it is 7 mm or less, we recommend periodic clinical and dermoscopic follow up.[29] One possible problem in using this algorithm is differentiation between regular and irregular fibrillar patterns. We defined the regular fibrillar pattern as follows: (i) overall arrangement of the fibrillar pigmentation is regular and symmetrical; (ii) thickness and length of each fibril composing the fibrillar pigmentation is mostly even; and (iii) end-points of the fibrils tend to be lined up on a straight line corresponding to a surface furrow (Fig. 7a). In some cases, horizontal

advancement of the cornified layer with the probe of a dermoscope changes the fibrillar pattern into the parallel furrow pattern.[15] Oblique dermoscopy is also helpful in the differentiation.[30] In contrast, in the irregular fibrillar pattern, overall arrangement of the fibrillar pattern is asymmetrical and irregular, the fibrils are arranged in a disorganized fashion, and end-points of the fibrils are not regularly lined up on a straight line (Fig. 7b).

Introduction of the category with no need for further follow up into the revised three-step algorithm is based on our concept of *de novo* histogenesis of acral melanoma.[4,24,31,32] In our estimation, clinical, histopathological and molecular findings support that acral melanoma arise *de novo*, not in association with a preexisting acral nevus. Although some temporal changes of dermoscopic features are observed in acral nevus,[21,22] transition from benign dermoscopic patterns to the parallel ridge pattern has never been observed.[29] This fact also strongly indicates that almost all acral melanomas arise de novo with the dermoscopic features of the parallel ridge pattern from the beginning and they are not in association with preexisting nevus.[24,32] In other words, acral nevus has virtually no risk of developing into melanoma.[24,29,31] Therefore, we believe that periodic follow up is not necessary for acquired melanocytic lesions, if they are definitely diagnosed as acral nevus with dermoscopy. Introduction of the category with no need for further follow up into the revised algorithm substantially reduces numbers of acral lesions to be followed up and relieves anxiety of patients bearing a benign melanocytic nevus on acral volar skin.[29]

Dermoscopy has opened a completely new horizon in effectively detecting early acral melanoma. Moreover, the three-step dermoscopic algorithm proposed by our group is highly helpful for clinicians in adequately managing melanocytic lesions on acral volar skin, the most prevalent site of malignant melanoma in non-Caucasians. Lastly, however, there is one important note to be aware of. We must know the parallel ridge pattern or its similar features could be detected in several benign conditions. They include volar pigmented lesions of Peutz–Jeghers or Laugier–Hunziker syndromes, acral pigmentation due to anticancer drugs, pigmented and ridged plantar warts, volar melanotic macules, so-called black heel (pebbles on the ridges pattern), occupational exposure to paraphenylenediamine, and so on.[13,33] However, these conditions can be rather easily differentiated from early acral melanoma by evaluating the clinical and dermoscopic characteristics, number of lesions (single or multiple), personal and/or family history, and other associated clinical signs and symptoms.

In conclusion, dermoscopy plays a powerful role in determining diagnosis of various kinds of acral pigmented lesions. Particularly, acral melanoma can be effectively detected in the early curable stages by using this rather simple diagnostic method.

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