Early detection of acral melanoma: A review of clinical, dermoscopic, histopathologic, and molecular characteristics

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Acral lentiginous melanoma is a distinct subtype of melanoma on acral skin. Patient presentation at later stages and delayed diagnosis by physicians contribute to a worse associated prognosis and survival rate. Despite our progress in understanding the key features of this disease, the diagnosis of early-stage acral melanoma is still challenging. It is essential to integrate clinical, dermoscopic, and histologic findings in the diagnosis of acral lentiginous melanoma. In addition, molecular studies can be helpful. In this review, we have summarized our current understanding of this disease entity from articles that were published between 1969 and 2018. We have outlined clinical and dermoscopic features as well as pathologic and molecular findings regarding acral melanoma and have presented an algorithm for diagnosis. Understanding and integrating these characteristics may assist clinicians in the early detection of acral melanomas. (J Am Acad Dermatol 2019;81:805-12.)

Key words: acral melanoma; algorithm; dermoscopy; diagnosis; foot; genetics; histopathology; melanoma; molecular; review.

Acral lentiginous melanoma (ALM) was first described Arrington et al as a distinct subtype of melanoma that has a predilection for acral areas, including the palms and soles.[1] It is the most common type of melanoma on acral skin. The terms *ALM* and *acral melanoma* (AM) are often used interchangeably. AM constitutes a greater proportion of melanomas occurring in nonwhites or people of color.[2-6] Age, Breslow thickness, and ulceration are poor prognostic factors for AM.[7,8] Low public awareness of ALM and delayed presentation to health care professionals contribute to delayed diagnosis and poor disease outcomes.[8-10] Understanding the characteristics of the early stages of AM is necessary to manage this disease at early and curable stages.

HISTORY

ALM was first reported in 1976 and is classified as a fourth subtype of cutaneous melanoma (CM), adding to the 3 previously described subtypes of CM: superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma.[11] Histologically, ALM demonstrates a diffuse proliferation of large atypical melanocytes along the dermoepidermal junction in a lentiginous growth pattern with marked acanthosis and elongation of the rete ridges.[1]

Risk factors for other subtypes of CM, such as sun exposure, fair skin type, family or personal history of melanoma, and pre-existing melanocytic nevi, are not applicable to AM.[12,13] The role of mechanical stress as a risk factor for AM has been suggested, and studies from Asian countries have shown a positive association between stress and development of AM.[14-17] However, data from the United States found no significant difference in the occurrence of AM on weight-bearing versus non–weight-bearing regions of the plantar surface of the foot.[18] Further investigation is necessary to elucidate the association of mechanical stress with AM.

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DIAGNOSIS

Diagnosis of early AM is challenging and requires the integration of clinical, histopathologic, dermoscopic, and molecular findings.

Clinical findings

AM in its early radial growth phase appears as an asymmetric brown macule or patch with irregular borders and variegated pigmentation.[19] Clinical guidelines for the early detection of plantar malignant melanomas were proposed by Saida et al in 1990 and included age older than 50 years and lesion diameter of 7 mm or more as risk factors.[20]

The utility of the standard ABCDE (asymmetric shape, border, color, diameter, evolution) criteria for melanocytic lesions has not been systematically investigated for AM. The acronym CUBED (colored, uncertain, bleeding, enlarged, delay) has been proposed to assist clinicians in assessing suspicious lesions specifically of the foot or nail unit.[21] It includes the presence of colored (C) or bleeding lesions (B) of uncertain diagnosis (U) that are enlarged (E) or deteriorate with delayed healing (D). The presence of 2 or more of these features suggests the need for further assessment and referral to experts for further diagnosis. However, the limitations of the acronym include the lack of specific morphologic criteria. In addition, there is no further study that validates the usefulness of the acronym in clinical settings.

Dermoscopic features

Dermoscopy has been widely used as an adjunctive visual assessment tool for pigmented skin lesions. AMs can demonstrate unique dermoscopic patterns, including the parallel ridge pattern (PRP) and irregular diffuse pigmentation.[22,23] In contrast, dermoscopic patterns of acral melanocytic nevi include the parallel furrow pattern, lattice-like pattern, and the fibrillar pattern. More than 75% of benign acral lesions exhibit 1 of these major patterns.[24] Compared with acquired acral nevi, congenital acral nevi are larger and more asymmetric, with a greater likelihood of exhibiting a blue-gray color or globules.[25]

CAPSULE SUMMARY

- Delayed detection of acral lentiginous melanoma results in poor patient outcomes. However, making the diagnosis at an early stage can be challenging.
- We have summarized current clinical guidelines on acral lentiginous melanoma, dermoscopic findings, histopathologic clues, and molecular findings. Integrating this information is required to diagnose this disease at an early, curable stage.

The PRP is the primary dermoscopic pattern in early lesions of AM (Fig 1).[26,27] This band-like pigmentation on the ridges of skin markings has widely distributed light brown pigmentation on early lesions and more focal dark brown to black pigmentation at more advanced stages.[24] PRP can also be observed in atypical melanosis of the foot (AMF) or atypical melanocytic hyperplasia, referring to atypically large pigmented lesions with slow evolution and subtle histopathologic atypia.[28-31] Later studies with consecutive biopsies revealed evolution of AMF lesions into overt AM in situ.[32,33] Therefore, AMF has now come to be regarded as an early phase of AM in situ.[32-35] We have shown that some ALMs have indolent progression with long radial growth phases.[9,36] Therefore, careful clinical and pathologic evaluation is warranted for slowly growing pigmented lesions with irregular borders on acral skin.

The demonstration of PRP on dermoscopic examination of AMF suggests that dermoscopic findings may precede the histopathologic changes of AM in situ. However, there are benign lesions that have been reported to demonstrate PRP on dermoscopic examination, including drug-induced acral pigmentation, subcorneal hemorrhage, and the lentigines of Peutz-Jeghers syndrome and Laugier-Hunziker syndrome.[37] Incorporation of other cutaneous findings and clinical history can assist in the differentiation of these entities from AM.

We recently reported that the dermoscopic findings of AM in situ differ from those of invasive AMs by demonstrating a reduced frequency of specific colors (red, blue, and white) and patterns (atypical vascular patterns, blue-white veil, and ulcers).[38] These observations may aid in the prediction of in situ versus invasive lesions before histopathologic evaluation of a lesion.

The 3-step algorithm. The first 3-step algorithm for the management of acquired melanocytic lesions on acral sites was proposed by Saida and Koga in 2007; it incorporates identification of PRP to assist in the differentiation of early AM from acral nevi.[39] According to the algorithm, acquired melanocytic acral lesions demonstrating PRP or a diameter of greater than 7 mm without typical benign pattern

Abbreviations used:

ALM: acral lentiginous melanoma
AM: acral melanoma
AMF: atypical melanoma of foot
CM: cutaneous melanoma
FISH: fluorescent in situ hybridization
PRP: parallel ridge pattern

should be subjected to biopsy for histopathologic evaluation whereas other lesions are to be clinically followed. In 2011, the 3-step algorithm was revised on the basis of the assumption that nearly all AMs arise de novo rather than in association with a preexisting acral nevus.[40] Therefore, the revised algorithm removed the recommendation for clinical follow-up for acral nevi with benign dermoscopic findings. Though the probability of a benign acral nevus developing into AM is debatable, this approach may reduce the burden on patients to clinically follow benign acral lesions. A recent single-center retrospective chart review found the 3-step algorithm to have a sensitivity of 80.0%, specificity of 87.8%, positive predictive value of 44.4%, and negative predictive value of 97.2%.[41] The algorithm missed 1 of 5 ALMs (a 6-mm, multicomponent, invasive melanoma), and the authors suggested a lack of sensitivity for the algorithm in diagnosing small multicomponent AMs. Of note, the fibrillar dermoscopic pattern was commonly misclassified as high-risk by physicians. Addressing this educational issue could reduce the number of biopsies performed on benign acral lesions.

The BRAAFF algorithm. As some AMs do not demonstrate PRP on dermoscopic examination, the BRAAFF checklist is proposed to improve the accuracy of dermoscopy for the diagnosis of AM.[42] The scoring system is composed of 4 positive patterns, including irregular blotches (1 point), PRP (3 points), asymmetry of structures (1 point), and asymmetry of colors (1 point). The scoring system also incorporates 2 negative features: presence of a parallel furrow pattern (−1 point) and fibrillar pattern (−1 point). Any lesion with total score of 1 or higher should be further evaluated for the diagnosis of AM. The sensitivity and specificity of the checklist were reported as 93.1% and 86.7%, respectively. Notable departures of this algorithm from the 3-step algorithm are the inclusion of blotches and asymmetry and the exclusion of lesion size.

Histopathology review

Although establishing a diagnosis of invasive AM is less difficult, diagnosing the early lesions of AM with subtle histopathologic features may be challenging. Excisional biopsy, which is the criterion standard for analysis of melanocytic lesions, is not routinely selected for AM because of their large size at presentation and the limited skin laxity of acral skin. Owing to the restricted skin reservoir on the acral skin, a moderate-size defect often cannot be closed primarily. Therefore, incisional biopsy or punch biopsy are often the initial diagnostic procedure. The skin of the palms and soles has a unique dermatoglyphic pattern consisting of furrows and ridges. Interpretation of melanocytic lesions on the palms and soles with sections cut perpendicular to the ridges and furrows is helpful in evaluating the distribution of melanocytes.[43] Consequently, when incisional biopsy is performed, it is preferable to make incisions perpendicular to the dermatoglyphics. When punch biopsy is performed, we recommend performing multiple punch biopsies of larger lesions to fully investigate pathologic changes. The biopsy specimen should include the most pigmented area, which is where the most atypical features may exist. When pathologic findings do not coincide with clinical findings, either further biopsy or a close follow-up should be cautiously considered.[44,45]

There are some architectural and cytologic features that can aid in the diagnosis of early ALM.[46] The architectural features of acral melanocytic lesions that are evaluated include (1) the tendency of melanocytes to proliferate singly or in nests, (2) melanocytic distribution, and (3) spread of melanocytes into upper layers of the epidermis. Cytologic features that are evaluted include (1) melanocyte size, (2) melanocyte shape, and (3) chromasia. In addition to these architectural and cytologic features, inflammatory change in the papillary dermis should be evaluated (Table I and Fig 1).

In the evaluation for cellular atypia and chromasia, the features of melanocyte and keratinocyte nuclei are compared. When melanocytic nuclei are hyperchromatic and larger than those of keratinocytes, the diagnosis of melanoma in situ should be considered.[46] Angulated and vertically arranged nuclei in addition to thick, elongated, and uneven dendrites are suggestive of malignancy. Melanocytes with thick or elongated dendrites reaching the superficial layers of the epidermis and the presence of dendritic processes that form webs around basal keratinocytes can be observed in AM, including in in situ lesions.[47] However, pagetoid spread can also be observed in more than one-third of benign acral nevi.[48,49] They are referred to as melanocytic acral nevi with intraepidermal ascent of cells (MANIAC).[49] Consequently, the sole presence of pagetoid melanocytes is insufficient for the diagnosis of AM in situ. In benign acral

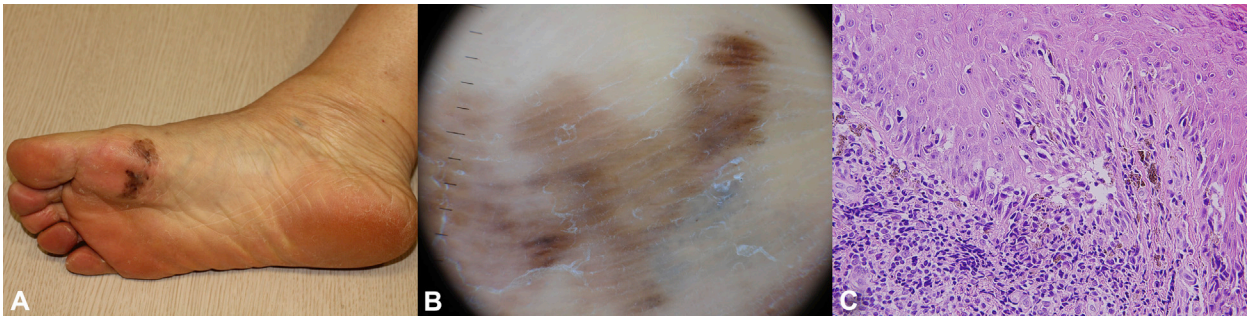

Fig 1. Acral lentiginous melanoma in situ. **A,** Irregular brown to black pigmented patch on the sole. **B,** Dermoscopy shows a parallel ridge pattern with asymmetric distribution of pigment. **C,** Histopathologic findings showing proliferation of scattered hyperchromatic melanocytes with lymphocytic infiltration in the papillary dermis. (**C,** Hematoxylin-eosin stain; original magnification: ×400.)

Table I. Histopathologic findings of acral nevus versus acral melanoma

Criteria		Acral nevus	Acral melanoma
Architectural	Nesting pattern	Predominance of melanocytic nests	Predominance of melanocytes as single units
		Cohesive, consistent in size, well-circumscribed, nonconfluent nests	Noncohesive, poorly circumscribed, confluent, and variably sized nests
	Melanocytic distribution	Generally symmetric distribution	Asymmetric distribution
		Uniform growths, equidistant from each other	Nonequidistant single units
	Spread of melanocytes	Distributed along the furrows/sulci	Distributed along the crests/ridge
	Pagetoid spread of melanocytes	Present (more than one-third)	Present but less prominent in early stages
		Lack of cytologic atypia in pagetoid cells	Cellular atypia in pagetoid cells
	Distribution of pigment in keratinic layer	Vertical column on top of furrow	Pigment found in confluent and wide areas of stratum corneum
Cellular	Size	Same size as or smaller than keratinocyte nuclei	Larger than surrounding keratinocytes
	Shape	Oval nuclei with smooth contour	Angulated nuclei
		Horizontal arrangement of nuclei	Vertical arrangement of nuclei
		Short and even dendrites	Thick, elongated, and uneven dendrites that form a web around basal melanocytes
	Chromasia	No hyperchromasia or mildly hyperchromatic cells that are only slightly darker in comparison with keratinocytes	Single cells with hyperchromatic, dark nuclei with prominent nucleoli
Inflammatory change		Usually absent	Lymphocytic infiltration in the papillary dermis; maybe absent in very early stages

nevi, cytologic atypia is not commonly observed in suprabasal melanocytes. In addition, there are more background melanocytic nests than single-ell proliferations. In AM, the pagetoid melanocytes may demonstrate an increased nuclear-to-cytoplasm ratio and/or dendritic or pleomorphic morphology and may have hyperchromatic nuclei.

One of the earliest signs of architectural atypia in AM is the diffuse proliferation of melanocytes as a single unit. When single cells coalesce, the resultant

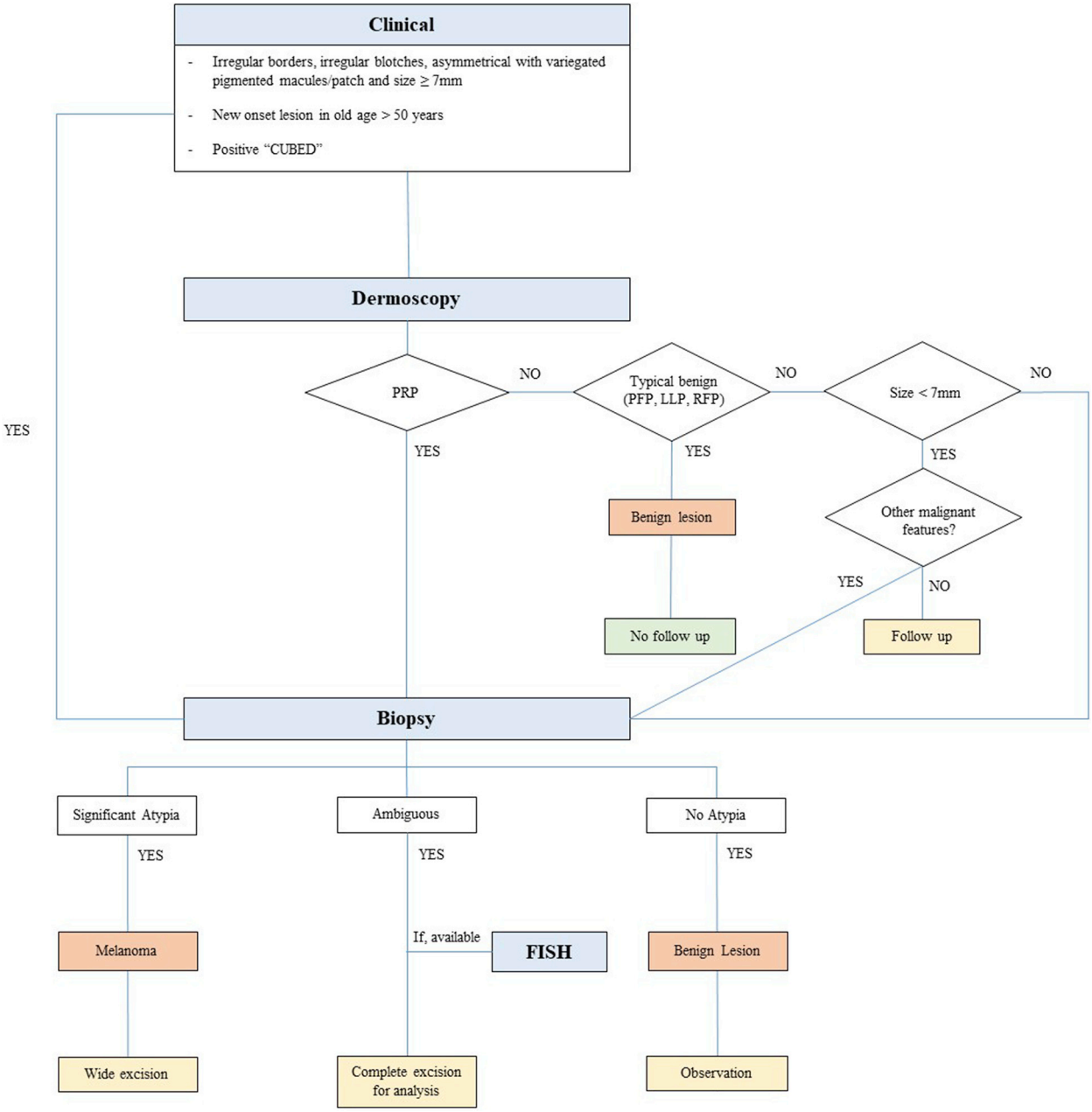

Fig 2. Our proposed algorithm for management of acral melanocytic lesions. FISH, fluorescence in situ hybridization; LLP, lattice-like pattern; PFP, parallel furrow pattern; RFP, regular fibrillar pattern.

nests tend to demonstrate variations in size, poor cohesion, and lack of circumscription.[46] The preferential proliferation of solitary melanocytes in the crista profunda intermedia can be a useful clue for the diagnosis of early-stage AM.[50] Distribution of pigment within the stratum corneum can also aid in the diagnosis of AM: in benign nevi, pigmentation is preferentially localized to the vertical columns representing the furrows. However, in the case of melanoma, pigmentation is mostly found within wide confluent areas of the stratum corneum.[46]

The presence of an inflammatory cell infiltrate, particularly the presence of lymphocytes, favors the diagnosis of AM in situ over benign acral nevi. Dermal inflammation is usually absent in benign acral nevi.[51] Therefore, dermal inflammation may be

a clue for the diagnosis of AM.[48] The presence of inflammation may be related to the immunogenicity of oncogenic atypical melanocytes.

Immunohistochemistry for melanocyte markers, including homatropine methylbromide 45, melan-A, and S-100 aids in the diagnosis of ALM. The presence of solitary melanocytes in the crista profunda intermedia on homatropine methylbromide 45 staining is suggestive of early-phase AM.[50]

Molecular findings

The results of a study by Sauter et al. implicate cyclin D1 (*CCND1*) as an oncogene in melanomas.[52] Its amplification was detected in AM more frequently than in other types of CM. The overexpression of *CCND1* in proliferating melanocytes as detected by fluorescence in situ hybridization (FISH) can be identified in the early radial growth phase of AM.[53] Aberrant amplification of *CCND1* can also be detected on isolated banal-appearing melanocytes surrounding an AM lesion.[54,55]

A 4-probe FISH assay can been useful in the diagnosis of AM.[56-58] The 4-color FISH assay targets 6p25 (ras responsive element binding protein 1 gene [*RREB1*]), centromere of chromosome 6 gene (*CEP6*), 6q23 (v-myb avian myeloblastosis viral oncogene homolog gene [MYB]), and 11q13 (cyclin D1 [CCND1]). The assay can be considered for lesions with subtle and indeterminate findings. A recent study reported a positive assay in 80% of definite AM in situ with a PRP pattern (4 of 5), in 80% of ambiguous cases with PRP but without sufficient histopathologic changes (4 of 5), and in 20% of junctional nevi with benign dermoscopic patterns (1 of 5). The results suggested that the application of FISH may enhance the diagnostic accuracy of early in situ AM when typical PRP is present with nondiagnostic histologic findings.[57]

The addition of other gene alterations to the 4-color FISH assay increases the sensitivity of this assay while maintaining its sensitivity.[56,58] Telomerase reverse transcriptase gene (*TERT*) and aurora kinase A gene (*AURKA*) copy number gains were found in 29.4% of AMs, and evaluating for amplification of these genes increased the sensitivity of the assay from 85.3% to 97% when compared with that of conventional 4-color FISH.[58] The addition of a 3-probe FISH assay targeting 8q24 (v-myc avian myelocytomatosis viral oncogene homolog gene [*MYC*]), 9p21 (cyclin dependent kinase inhibitor 2A gene [*CDKN2A*]), and *CEP9* (centromere 9) to the 4-color FISH assay increased the sensitivity from 70.5% to 88.6%.[56]

Genetic mutations. Bioinformatics data from whole genome sequencing of melanoma revealed AMs and mucosal melanomas to have a lower mutational burden with a higher structural variation than do other subtypes of CM.[59] B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*), NRAS proto-oncogene, GTPase gene (*NRAS*), and neurofibromin 1gene (*NF1*) were significantly mutated in AM versus in other subtypes.[59] Mutation ranges were between 3.6% and 33.3% for *BRAF* and between 3% and 47% for *NRAS*.[60] KIT proto-oncogene receptor tyrosine kinase gene (*KIT*) mutations were also common in AM, ranging in frequency between 2.9% and 23%.[59,61-65] *KIT* mutations have been associated with advanced Clark level and are frequently coamplified with platelet derived growth factor receptor alpha gene (*PDGFRA*).[59,61]

Because of the reduced exposure of volar skin to ultraviolet radiation, distinct non−ultraviolet-mediated alterations have been speculated to play a major role in the pathogenesis of AM. A recent study suggests that melanomas on dorsal acral skin demonstrate molecular findings that are distinct from those of volar or ungual melanomas. Specifically, *BRAF* mutations were less likely to occur among volar or ungual AMs than among dorsal acral lesions.[63]

Mutations in *TERT* promoter in AM range in frequency between 6% and 9%.[61,66,67] Total *TERT* aberrations were found in 41% of 34 patients; subsequent in vitro findings demonstrated the cytotoxic effect of TERT inhibitors in AM cells. Though the development of new treatments targeting specific genetic aberration is promising, the utility of genetic information in establishing the diagnosis of early-stage AM has not been sufficiently elucidated.

CONCLUSIONS

Though the criterion standard for the diagnosis of ALM is histopathologic analysis, the integration of clinical and dermoscopic features of ALM enhances diagnostic accuracy (Fig 2). Immunohistochemical studies and molecular testing can assist in distinguishing early-stage AMs from benign acral lesions. Understanding and integrating these features can reduce misdiagnosis and allow earlier detection of AM. Future studies correlating histopathologic and molecular findings of early-stage AM with clinical and dermoscopic patterns will further assist physicians in making an early diagnosis.

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