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Atypical Melanosis on Acral Skin or Early Acral Lentiginous Melanoma? Reappraising an Ambiguous Concept in Acquired Acral Pigmented Lesions

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1 | Background

Acral lentiginous melanoma (ALM), first described by Reed et al. in 1976, is a histopathologic subtype of cutaneous melanoma (CM) that arises on the palms, soles, or within the nail apparatus [1]. Although ALM represents only a small percentage of all CMs in populations predominantly of European descent, it is the most common subtype in most Latin American, African, and Asian countries, where other histopathologic variants are markedly underrepresented [2]. The fact that these slow-growing tumors often develop in "hidden" locations and remain clinically subtle during their early stages hinders early clinical detection, likely contributing to their poorer overall prognosis compared to other CM subtypes [2–4].

Not only that, but early histopathologic diagnosis of ALM is particularly challenging. In this sense, excisional biopsy—the gold standard for histopathological evaluation of melanocytic neoplasms—is often not performed at the initial assessment of ALM due to the large lesion size at presentation and the anatomic peculiarities of acral skin, which can limit primary closure even for relatively small lesions [3]. Consequently, pathologists frequently receive partial samples from slow-growing tumors that, despite their sometimes large size, may still be in situ, with no clear evidence of invasion. Likewise, the diagnosis of early ALM often relies on subtle histopathologic features, particularly a paucicellular proliferation of nearly typical melanocytes along the epidermal basal layer. Therefore, definitive diagnosis must be based on a close correlation of clinical and dermatoscopic findings [5].

Otherwise, because these microscopic findings may be insufficient for the pathologist to confidently render a diagnosis of melanoma, misinterpretation of such subtle features may lead to insufficient or inappropriate management under ambiguous diagnostic labels such as "atypical melanosis" [5, 6]. As a result, diagnostic delay in this context can lead to more complex reconstructive procedures, increased morbidity, long-term disability, and higher healthcare costs. Furthermore, prognosis in patients progressing to advanced stages (III–IV) may be severely affected by two main factors: (1) the low prevalence of *BRAF* mutations (approximately 15%–21%) in acral CMs [7], which limits first-line therapeutic options to immunotherapy; and (2) the lower effectiveness of both anti-PD-1 monotherapy and combined anti-CTLA-4/anti-PD-1 therapy in acral CM, with lower response rates, progression-free survival, and overall survival compared with other CM subtypes, probably due to a lower mutational burden [8].

Given these challenges, promoting early diagnostic strategies and clarifying certain clinico-dermatoscopic and histopathologic concepts are of utmost importance in the specific management of ALM. The aim of this article is to highlight the need for multidisciplinary collaboration in the diagnosis of very

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early ALMs, in which histopathologic criteria alone may be insufficient for non-expert pathologists and could lead to misdiagnosis. To this end, we present two illustrative cases of early ALM of the hands, in which multidisciplinary evaluation was essential to reach a final diagnosis, and we review additional diagnostic clues described in the literature that may be useful in similar cases.

2 | Case 1

A 52-year-old woman with skin type IV presented with a slowly but continuously enlarging pigmented lesion, 11 mm in diameter, on the second finger of her right hand, which had been present for at least 2 years (Figure 1A1). Dermatoscopic examination revealed irregular diffuse pigmentation and a

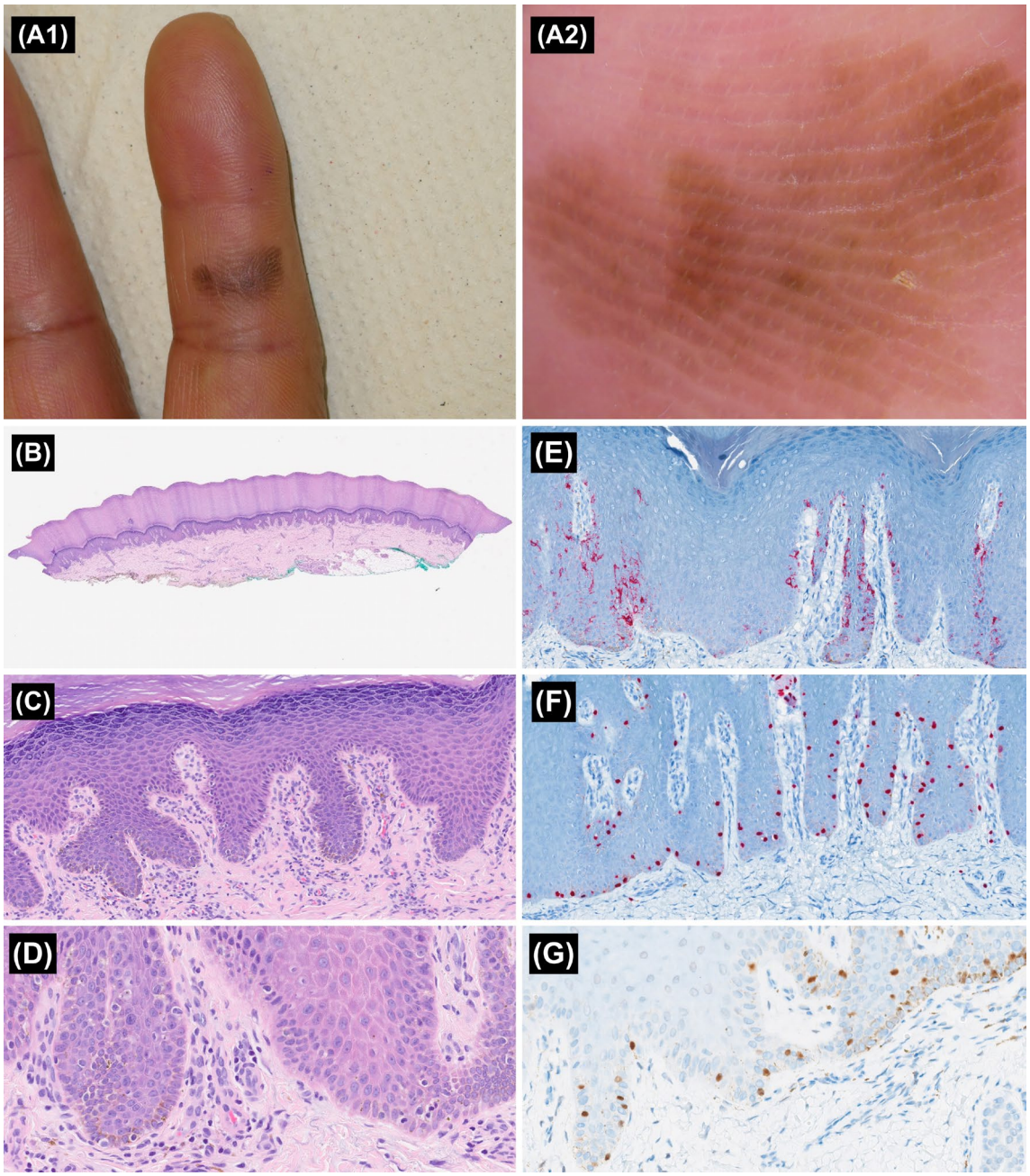

FIGURE 1 | (A1) Pigmented lesion located on the second finger of a 52-year-old woman. (A2) Dermatoscopic examination revealed irregular diffuse pigmentation and a characteristic *parallel ridge pattern* (Dermatoscope Dermlite DL200 hybrid attached to a Panasonic Lumix tz90 digital camera). (B) Panoramic view of the complete excision specimen (H&E, ×20). (C) Epidermal acanthosis with irregular elongation of the rete ridges. At this magnification, only slight proliferation of melanocytes, hyperpigmentation of the basal layer, and mild inflammatory infiltrates in the papillary dermis are present (H&E, ×200). (D) High-power view showing a paucicellular lentiginous proliferation of melanocytes without significant cytologic atypia (only mild hyperchromasia) (H&E, ×400). (E, F) HMB-45 and SOX-10 immunostaining, respectively, demonstrate an irregular distribution of melanocytes with partial confluence and occasional thick dendrites limited to the lower epidermal tier (×200). Note in (E) how the melanocytic proliferation is distributed preferentially along the *crista profunda intermedia*, which corresponds to the *parallel ridge pattern* in dermatoscopy. (G) PRAME immunostaining showing positive nuclear expression (×400).

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parallel ridge pattern (PRP) (Figure 1A2). Histopathologic evaluation of an initial incisional biopsy demonstrated a mild, non-continuous proliferation of melanocytes without atypia, associated with keratinocyte hyperpigmentation and dermal melanophages.

Because of clinicopathologic discrepancies and the absence of definitive histopathologic evidence of malignancy, the lesion was completely excised. The excision specimen showed a paucicellular lentiginous proliferation of melanocytes without significant cytologic atypia (Figure 1B–D). HMB-45 immunostaining revealed partial confluence of this proliferation, and "Preferentially Expressed Antigen in Melanoma" (PRAME) staining was positive (Figure 1E–G). Based on the combined clinical, dermatoscopic, histopathologic, and immunohistochemical findings, a final diagnosis of early in situ ALM was established, and wide local excision was performed.

3 | Case 2

A 55-year-old woman, also with skin type IV, presented with a slowly enlarging pigmented lesion, 7 mm in diameter, on her left thumb (Figure 2A1). Dermatoscopy revealed a clear-cut PRP

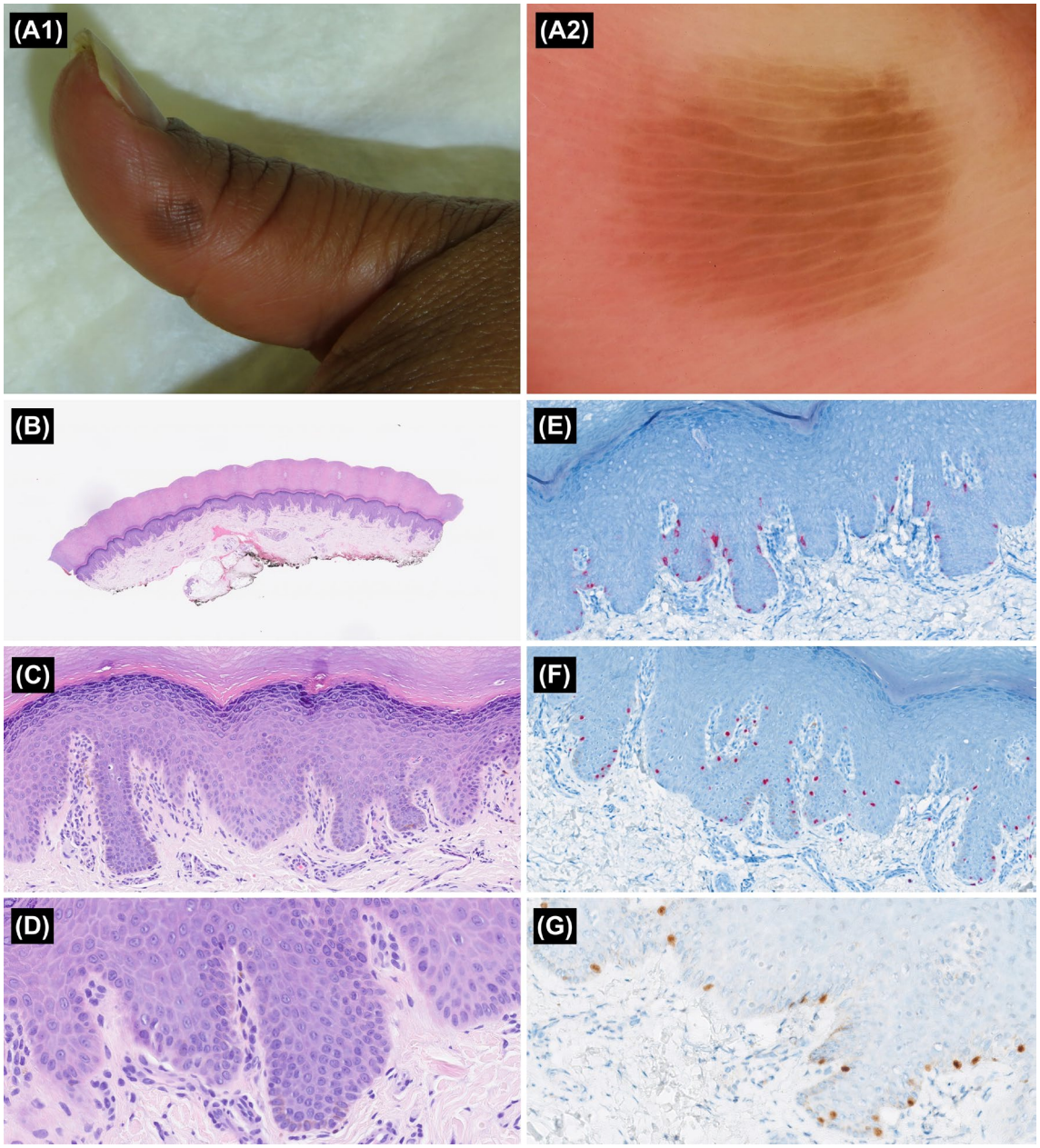

FIGURE 2 | (A1) Pigmented lesion located on the left thumb of a 55-year-old woman. (A2) Dermatoscopic examination revealed a clear-cut *parallel ridge pattern* (Dermatoscope DZ-D100, Casio Computer Co. Ltd., Tokyo, Japan). (B) Panoramic view of the excision specimen (H&E, ×20). (C) Epidermal changes similar to those observed in the previous case, although even more inconspicuous (H&E, ×200). (D) At higher magnification, no remarkable melanocytic proliferation is observed (H&E, ×400). (E, F) Melan-A and SOX-10 immunostaining, respectively, demonstrate a non-equidistant proliferation of melanocytes with only a few foci showing a tendency toward confluence. No thick dendrites or cytologic atypia are evident (×200). (G) PRAME immunostaining shows strong nuclear positivity (×400).

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(Figure 2A2), prompting direct excisional biopsy. Hematoxylin and eosin (H&E) examination revealed no significant pathologic abnormalities (Figure 2B–D). However, SOX-10 and Melan-A immunostaining disclosed a subtle single-cell proliferation of non-equidistant melanocytes with irregular distribution, slightly enlarged nuclei, and thick dendrites. PRAME expression was strongly positive (Figure 2E–G). Accordingly, a final diagnosis of early ALM was made, and wide excision was performed.

4 | Discussion

The term "atypical melanosis of the foot" (AMOF) as first introduced by Nogita et al. [6] in 1994 to describe clinically atypical melanocytic lesions resembling ALM but characterized histopathologically by a mild, focal, single-cell melanocytic hyperplasia with minimal cytologic atypia—similar to the two illustrative cases presented here, although both were located on the hands. The authors differentiated these lesions from early ALM based solely on the absence of definitive histologic features of malignancy. Several years earlier, Saida et al. [9] had classified in situ ALM into three progressive phases, with stage I corresponding to a slight increase in the number of melanocytes—some with atypical nuclei—arranged as solitary units along the basal layer of the epidermis. Notably, this phase differs from the AMOF concept only in the degree of melanocytic atypia, which may be subtle and subject to interobserver variability. Consistent with this, Oh et al. reported an invasive ALM that developed within a long-standing irregular pigmentation initially diagnosed histologically as AMOF [10]. This observation aligns with our own experience, as we have frequently observed similar subtle histologic alterations in the vicinity of unequivocally invasive ALMs (Figures 3 and 4). For this reason, several authors have proposed that ambiguous terms such as "AMOF" or "atypical hyperplasia" should be abandoned, since these lesions most likely represent the earliest histologic stage of ALM [5, 11–13]. Indeed, such lesions could reasonably correspond to a "Phase 0" in the classification of in situ ALM proposed by Saida et al. [9] Moreover, this terminology overlooks the fact that acral skin on the hands, although less frequently affected, may also harbor these lesions—as in the cases described herein.

The concept "atypical intraepidermal melanocytic proliferation" (AIMP) has also been proposed as a useful general term for melanocytic proliferations of uncertain biological behavior that do not allow a definitive diagnosis of melanoma from a histopathological point of view. Although this term may be appropriate for lesions similar to those we have presented, it should be clear that clinically/dermatoscopically concerning lesions classified under this diagnostic category should almost always be treated as a possible melanoma. This logic should be applied especially in single partial biopsies of large lesions, in which case multiple sampling or complete excision should be recommended in the pathology report. In fact, several studies have reported a significant rate of diagnostic change of AIMP to melanoma following conventional excision and immunohistochemistry, ranging from 4.2% to 21.3% [14, 15]. Furthermore, acral location (OR 9.24, 95% CI 2.18, 39.24; $p = 0.001$) and previous punch biopsy (OR 6.06, 95% CI 1.95, 18.86; $p = 0.013$) have been associated with diagnostic change [14].

From a clinical standpoint, we must start from two key concepts: those acquired acral pigmented lesions that are (1) larger than 7 mm and/or (2) that appear in patients older than 50 years should be interpreted in the first instance as a possible ALM [16]. Moreover, the advent of dermatoscopy has been a turning point in the early detection of ALM. The so-called PRP is the cornerstone of dermatoscopic diagnosis of ALM, achieving 99–100% specificity compared to acral nevi [17, 18]. Histopathologically, the PRP corresponds to a band-like pigmentation on the ridges of the skin markings, resulting from preferential proliferation of melanocytes along the *crista profunda intermedia*, located immediately beneath the ridges [19]. It is worth noting that this pattern has also been described in single-cell lentiginous melanocytic proliferations previously categorized as AMOF [12, 20], and more rarely in drug-induced pigmentation, subcorneal hemorrhage, or Laugier–Hunziker syndrome [21]. However, Saida

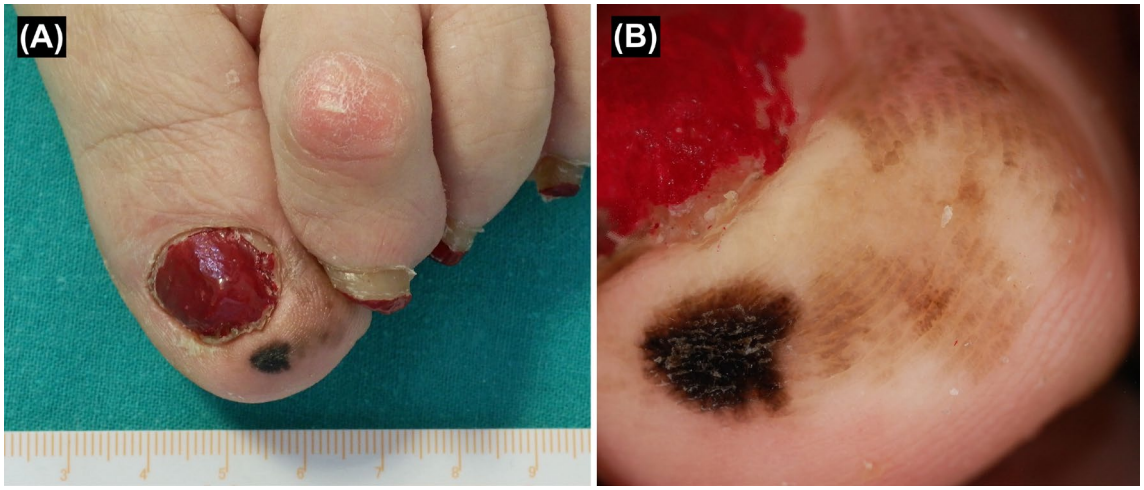

FIGURE 3 | (A) Long-standing asymmetric pigmented lesion on the great toe of an 80-year-old woman. (B) Dermatoscopic examination revealed an irregular blotch, irregular diffuse pigmentation, and a prominent *parallel ridge pattern* (Dermatoscope DZ-D100, Casio Computer Co. Ltd., Tokyo, Japan).

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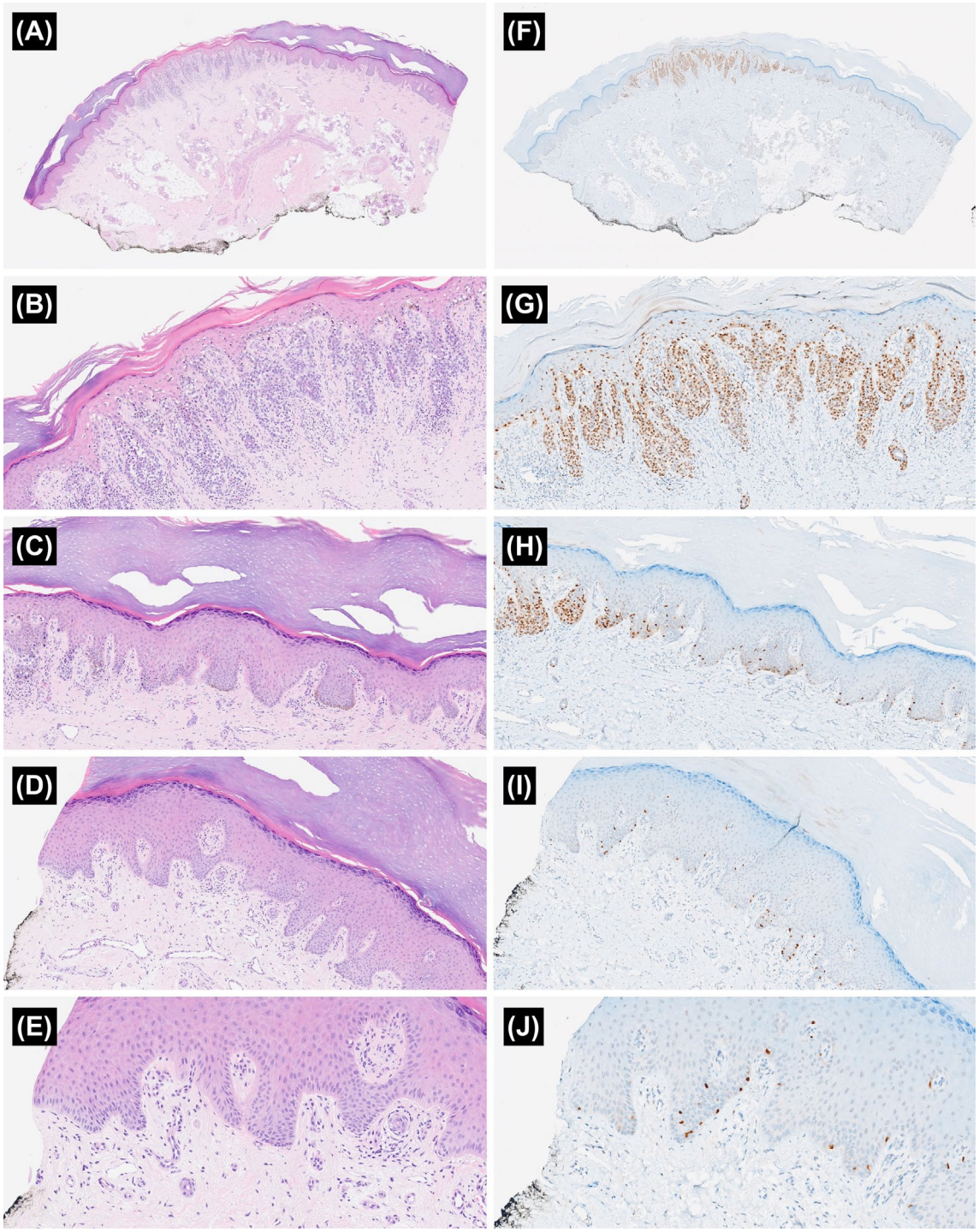

FIGURE 4 | (A) Panoramic view of a section from the excision specimen (H&E, ×20). (B–D) Consecutive images from the invasive central component toward the margin, showing a progressive decrease in melanocytic proliferation and a highly cellular proliferation with pagetoid upward migration in the central area (B); transition to a less cellular lentiginous component (C); and only a slight increase in melanocytes at the periphery (D) (H&E, ×100). (E) At higher magnification, a barely noticeable melanocytic proliferation is observed in one of the lateral margins (H&E, ×200). (F–I) PRAME immunostaining demonstrates strong nuclear positivity in the same areas shown in the corresponding H&E sections (x20–×200). (J) The subtle melanocytic proliferation shown in (E) is also highlighted by PRAME immunostaining (×200). Note that the invasive part of the lesion corresponds dermatoscopically to the *irregular blotch*, while the paucicellular lentiginous proliferation of melanocytes has its dermatoscopic equivalent in the *parallel ridge pattern* (Figure 3).

et al. [18] identified this pattern in only 6 of 609 (1.0%) acral nevi, reinforcing from a clinico-dermatoscopic perspective the view that such incipient lesions represent the earliest histologic stage of ALM.

In addition, several ancillary techniques (immunohistochemistry and molecular tests) can aid pathologic diagnosis. A recent single-center cohort study by Zheng et al. [22], analyzing 122 acral specimens, reported a sensitivity of 72.5% and a specificity

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TABLE 1 | Summary of the main features of acral lentiginous melanoma (ALM) in its earliest stages [3, 5, 16, 19, 22–27].

Clinical data	Dermatoscopic features	Histopathological findings	Immunohistochemistry/ FISH
Acquired pigmented lesion Irregularly pigmented Size ≥ 7 mm Appearance at ≥ 50 years	"Parallel ridge pattern" Irregular diffuse pigmentation BRAAFF checklist[a]	(Sometimes subtle) proliferation of melanocytes as non-equidistant single units Absence of nests Clear-cut cellular atypia may be absent Preferential proliferation in the crista profunda intermedia	PRAME + Loss of p16 CCND1 amplification

Abbreviations: CCND1: cyclin D1; PRAME: preferentially expressed antigen in melanoma.
[a]BRAFF checklist: a score of +1 or higher should raise suspicion of ALM (irregular blotch: +1; parallel ridge pattern: +3; asymmetry of structures: +1; asymmetry of colors; +1; parallel furrow pattern: −1; fibrillar pattern: −1).

of 97.4% for PRAME positivity in in situ acral melanomas. When combined PRAME-positive/p16-negative status was used, specificity reached 100%, albeit with lower sensitivity (22.5%). The diagnostic utility of PRAME immunostaining and p16 loss in differentiating acral melanocytic lesions has also been highlighted in previous studies [23, 24]. Finally, amplification of *cyclin D1* (*CCND1*), detectable by fluorescence in situ hybridization (FISH), can be detected even at a very early progression phase of ALM [25]. In fact, Ogata et al. found FISH positivity in 4/5 (80%) acral lesions analogous to these two cases, that is, showing a "PRP" but histologically characterized by insufficient melanocyte proliferation and atypia to diagnose malignant melanoma using H&E staining [26].

5 | Conclusion

Early-stage ALM may display extremely subtle histopathologic features, often limited to mild lentiginous melanocytic hyperplasia without significant cytologic atypia. In such cases, a definitive diagnosis cannot rely solely on histopathologic findings. Instead, a comprehensive evaluation integrating clinical, dermatoscopic, and histopathologic data—supplemented by immunohistochemistry and molecular analyses when available—is essential (Table 1). Multiple or larger incisional biopsies are recommended for large lesions where primary reconstruction after an excisional biopsy would be complex. Because these lesions may exhibit inconspicuous histopathologic changes even when large, observation alone is not recommended, and wide local excision according to clinical guidelines should remain the standard of care. For all these reasons, ambiguous terms such as *"AMOF"* or *"atypical hyperplasia"* should be definitively abandoned.

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Disclosure

All people designated as authors had participated in the work to take public responsibility in its contents. The authors declare that artificial intelligence has not been used for collecting, analyzing or interpreting the data of this manuscript.

Ethics Statement

This case series was conducted in accordance with the Declaration of Helsinki. Written informed consent has been obtained from the patient for the use of image and publication of his case details.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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