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Acral Lentiginous Melanoma: A Comprehensive Review of Epidemiology, Pathophysiology, Clinical Presentation, and Therapeutic Advances

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ABSTRACT

Acral lentiginous melanoma (ALM) is a distinct and aggressive subtype of melanoma that disproportionately affects individuals with darker skin tones, representing a unique clinical and biological entity within the broader spectrum of cutaneous melanoma. Although ALM accounts for a relatively small percentage of melanomas globally, it is the most common subtype in non-Caucasian populations. The pathogenesis of ALM is characterized by genetic alterations distinct from other melanoma subtypes, often involving mutations in KIT and focal amplifications, rather than BRAF or NRAS mutations. Clinically, ALM frequently arises on acral surfaces, including palms, soles, and subungual regions, often presenting at an advanced stage due to delayed diagnosis. This review aims to provide a detailed examination of the epidemiology, molecular pathophysiology, clinical manifestations, and diagnostic approaches of ALM, while also highlighting emerging therapeutic strategies, including surgical management, targeted therapy, and immunotherapy. Recognizing the unique challenges associated with ALM is critical for improving early detection, tailoring treatment strategies, and ultimately enhancing patient outcomes.

KEYWORDS: Acral lentiginous melanoma, melanoma subtypes, KIT mutations, acral melanoma, cutaneous oncology, immunotherapy, targeted therapy, melanoma diagnosis.

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INTRODUCTION

Melanoma is a malignant neoplasm arising from melanocytes, predominantly found in the skin but also present in mucosal and ocular tissues. Among its various subtypes, acral lentiginous melanoma (ALM) occupies a distinctive position due to its epidemiological, clinical, and molecular characteristics. Initially described by Reed in 1976, ALM primarily affects acral sites, including the palms, soles, and subungual regions, and is often associated with a poorer prognosis compared to other melanoma subtypes.1,2

Despite constituting only 2-3% of melanomas in Caucasian populations, ALM represents the predominant subtype among individuals of Asian, African, and Hispanic descent, underscoring significant racial and ethnic disparities in melanoma incidence. The pathophysiology of ALM is distinct from that of cutaneous melanoma linked to ultraviolet (UV) radiation exposure, as it often arises in UV-protected areas. Genetic studies have identified unique molecular alterations in ALM, including frequent KIT mutations, amplifications of cyclin D1, and loss of PTEN, which differ significantly from the BRAF and NRAS mutations commonly observed in other melanomas.1,2

Clinically, ALM poses diagnostic challenges due to its insidious onset and atypical presentation, often leading to delayed diagnosis and advanced disease at presentation. The characteristic lentiginous proliferation of atypical melanocytes observed histologically, coupled with its predilection for acral surfaces, underscores the importance of heightened clinical suspicion and robust diagnostic tools, including dermoscopy, biopsy, and molecular analysis.1,2

Therapeutically, the management of ALM presents unique challenges. While surgical excision remains the cornerstone of treatment, advanced cases often necessitate adjuvant therapies, such as targeted therapy and immunotherapy.

Recent advances in molecular profiling have opened avenues for personalized treatments targeting the specific genetic alterations in ALM, although outcomes remain less favorable compared to other melanoma subtypes.1,2

This article aims to provide a comprehensive review of ALM, encompassing its epidemiology, molecular basis, clinical characteristics, and evolving therapeutic landscape. By addressing the unique aspects of ALM, this review seeks to enhance understanding and inform strategies for improved patient care in this challenging melanoma subtype.2,3

EPIDEMIOLOGY

Acral lentiginous melanoma (ALM) represents a rare but clinically significant subtype of cutaneous melanoma, characterized by its predilection for acral surfaces such as the palms, soles, and subungual regions. While its overall incidence is low in comparison to other melanoma subtypes such as superficial spreading melanoma or nodular melanoma, ALM demonstrates unique epidemiological trends, particularly in its disproportionate prevalence among non-Caucasian populations.2,3

Globally, melanoma is predominantly associated with populations of European descent, with ultraviolet (UV) radiation exposure serving as a major etiological factor. However, ALM diverges markedly from this pattern. In Caucasian populations, ALM accounts for approximately 2-3% of all melanomas. In contrast, it is the most prevalent melanoma subtype among individuals of Asian, African, and Hispanic ancestry, comprising up to 60-75% of all melanomas diagnosed in these groups. This racial and ethnic disparity underscores the distinct etiopathogenesis of ALM, as it arises in areas typically shielded from UV radiation.3,4

The overall incidence of ALM remains low, with population-based studies estimating a rate of 0.5-1 case per million annually. Despite its rarity, ALM poses a significant public health concern due to its association with delayed diagnosis, advanced stage at presentation, and relatively poor prognosis. In non-Caucasian individuals, melanoma is frequently underrecognized, in part due to misconceptions about the susceptibility of darker skin to melanoma. This delay in recognition is compounded by the insidious growth pattern of ALM, which can mimic benign lesions such as plantar warts, fungal infections, or traumatic nail injuries.4

Age and sex distribution also exhibit notable patterns in ALM epidemiology. The median age at diagnosis is typically older than for other melanoma subtypes, with most cases occurring in individuals over the age of 50. There is a slight male predominance in some studies, although this varies by population. Additionally, environmental factors and genetic predispositions play less prominent roles in ALM development compared to UV-related melanomas, further distinguishing its epidemiological profile.4

Notably, ALM's prevalence in non-Caucasian populations raises critical questions about healthcare access and equity. Studies have consistently shown that patients with ALM, particularly those of minority racial and ethnic groups, are more likely to present with advanced disease and have worse survival outcomes. Socioeconomic barriers, limited access to dermatological care, and lower awareness of melanoma risk in darker-skinned populations contribute to these disparities.4

Epidemiological studies have also revealed geographical variations in ALM incidence. For example, in East Asia, ALM constitutes the majority of melanoma cases, whereas in sub-Saharan Africa, it represents a significant proportion of melanomas diagnosed in the context of HIV-associated immunosuppression. These regional differences highlight the interplay between genetic, environmental, and healthcare system factors in shaping ALM's epidemiological landscape.5

Given the distinct epidemiology of ALM, efforts to improve early detection and diagnosis in high-risk populations are paramount. Public health campaigns emphasizing the importance of foot and nail examinations, particularly in non-Caucasian individuals, and enhanced training for clinicians in recognizing atypical presentations of melanoma are critical steps toward reducing the burden of this aggressive disease. Additionally, further epidemiological research is needed to elucidate the genetic and molecular factors that underlie ALM's predilection for certain populations, which may inform the development of targeted prevention and treatment strategies.5

CLINICAL MANIFESTATIONS

Acral lentiginous melanoma (ALM) is a distinct and clinically challenging subtype of melanoma, characterized by its predilection for acral sites, including the palms, soles, and subungual regions. The clinical presentation of ALM is highly variable, often resulting in delayed diagnosis and advanced disease at the time of presentation. Understanding its unique clinical manifestations is essential for timely recognition and effective management.5

Cutaneous Features

ALM typically begins as a slowly expanding macule or patch with irregular pigmentation. The lesion often appears on non-hair-bearing acral surfaces, such as the plantar aspect of the foot or the palm of the hand. The early-stage lesion is frequently asymmetric, with poorly defined borders and a heterogeneous mix of colors, including brown, black, gray, and, in some cases, amelanotic areas that appear pink or flesh-toned. The lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction accounts for its characteristic clinical and histological features.6

The radial growth phase of ALM can persist for months to years, during which the lesion remains confined to the epidermis. However, as the tumor progresses to the vertical growth phase, it begins to invade deeper dermal layers, forming nodules or ulcers. Advanced lesions are often raised, firm, and associated with irregular surface changes, including

hyperkeratosis or fissuring. Ulceration and bleeding are common in advanced cases, particularly when the lesion is subjected to mechanical trauma.6

Subungual Involvement

A hallmark feature of ALM is its propensity to involve the subungual region, where it presents distinct diagnostic challenges. Subungual ALM often manifests as a pigmented streak or band (melanonychia) along the longitudinal axis of the nail. This pigment may vary in color, from light brown to black, and is frequently irregular in width and intensity. The Hutchinson's sign—pigmentation of the periungual skin adjacent to the nail plate—is a key diagnostic clue, albeit not pathognomonic, as it can also be seen in benign conditions.7

As the disease progresses, subungual ALM may lead to nail dystrophy, including splitting, thickening, or destruction of the nail plate. Pain and secondary infections may develop in advanced cases, further complicating the clinical picture. Subungual ALM is often mistaken for benign conditions such as onychomycosis, hematomas, or trauma-induced changes, contributing to diagnostic delays.7

Pain and Functional Impairment

Patients with ALM frequently report pain, particularly when the lesion is located on weight-bearing areas such as the plantar surface of the foot. Pain may result from tumor invasion into dermal structures, nerve involvement, or secondary complications such as ulceration and infection. Functional impairment is also a significant concern, especially for lesions on the palms or soles, where mechanical pressure exacerbates symptoms and interferes with daily activities.8

Regional and Systemic Involvement

Advanced ALM often presents with regional lymphadenopathy due to metastasis to draining lymph nodes. Palpable, firm, and occasionally tender lymph nodes may be detected on physical examination. In cases of distant metastasis, symptoms vary depending on the organs involved, commonly including the lungs, liver, and brain. Systemic manifestations such as fatigue, weight loss, and night sweats may also occur in advanced stages.8

Challenges in Early Recognition

The clinical presentation of ALM is frequently subtle in its early stages, resembling benign conditions such as plantar warts, calluses, tinea pedis, or traumatic nail injuries. This mimicry contributes to significant diagnostic delays, particularly in non-Caucasian populations, where awareness of melanoma risk is low. The lack of a clear association with UV exposure further reduces clinical suspicion, even among healthcare providers.9

Importance of Dermoscopic Examination

Dermoscopy plays a pivotal role in the clinical evaluation of ALM, aiding in the identification of specific features such as parallel ridge patterns, irregular pigmentation, and atypical vascular structures. Subungual ALM, in particular, benefits from dermoscopic evaluation, which can differentiate melanonychia caused by ALM from benign conditions such as melanocytic nevi.10

The clinical manifestations of ALM encompass a wide spectrum of features, ranging from subtle pigmentation changes to aggressive, ulcerated lesions. Its predilection for acral and subungual regions, combined with its insidious onset and mimicry of benign conditions, underscores the importance of heightened clinical vigilance and comprehensive diagnostic evaluation. Recognizing the clinical hallmarks of ALM and employing tools such as dermoscopy are critical for improving early detection and reducing the morbidity and mortality associated with this aggressive melanoma subtype.10

Diagnostic Methods

The diagnosis of acral lentiginous melanoma (ALM) presents unique challenges due to its atypical clinical presentation and frequent resemblance to benign conditions. Early and accurate diagnosis is crucial, as ALM is often identified at an advanced stage, adversely affecting prognosis. A systematic approach combining clinical evaluation, dermoscopy, imaging, histopathology, and molecular studies is essential for the comprehensive assessment of this melanoma subtype.11

Clinical Examination

The diagnostic process begins with a thorough clinical evaluation. ALM typically manifests as a pigmented lesion on the palms, soles, or subungual areas, with features such as asymmetry, irregular borders, and heterogenous coloration. Subungual ALM often presents as melanonychia or pigmentation extending to the periungual skin (Hutchinson's sign). A detailed history should assess lesion evolution, presence of pain, ulceration, or bleeding, and risk factors, including family history of melanoma or previous trauma to the site.11

While clinical suspicion is essential, the subtlety of early ALM can result in misdiagnosis, as the lesion may mimic benign conditions such as warts, calluses, fungal infections, or subungual hematomas. Thus, clinical examination must be complemented with diagnostic tools.11

Dermoscopy

Dermoscopy is a cornerstone in the evaluation of pigmented lesions and plays a critical role in distinguishing ALM from benign acral lesions. Key dermoscopic features of ALM include:

1. **Parallel Ridge Pattern**: A hallmark finding in ALM, characterized by pigmented lines along the ridges of the acral skin, as opposed to the benign parallel furrow pattern observed in melanocytic nevi.11

2. **Irregular Pigmentation**: Uneven distribution of colors such as brown, black, gray, or even amelanotic areas.11
3. **Atypical Vascular Patterns**: Non-specific, irregular blood vessels or dotted vessels in areas lacking pigmentation.12
4. **Subungual Lesions**: Longitudinal melanonychia with irregular width, color heterogeneity, and extension of pigmentation to the periungual area.

Dermoscopy significantly enhances diagnostic accuracy, especially when interpreted by experienced clinicians. However, it should be noted that certain amelanotic or hypo-pigmented ALMs may lack distinct dermoscopic features, necessitating further evaluation.12

Histopathological Analysis

Histopathology remains the gold standard for diagnosing ALM. A biopsy of the lesion, preferably an excisional biopsy with a margin of normal tissue, is critical for definitive diagnosis. For subungual lesions, nail plate removal or longitudinal biopsy may be required to obtain adequate tissue.12

Histologically, ALM is characterized by:

1. **Lentiginous Proliferation**: Atypical melanocytes arranged in a single layer or nests along the basal epidermis, often extending down adnexal structures.12
2. **Pagetoid Spread**: Upward migration of atypical melanocytes into the epidermis.
3. **Dermal Invasion**: In the vertical growth phase, tumor cells invade the dermis, forming nests and exhibiting mitotic activity.12
4. **Amelanotic Areas**: In some cases, particularly in amelanotic ALM, there may be minimal pigmentation, complicating histological assessment.

Immunohistochemical staining is frequently employed to confirm the melanocytic origin of the lesion, with markers such as S-100, HMB-45, and Melan-A.12

Imaging Studies

Advanced imaging techniques are employed to assess the extent of local invasion and metastasis. These include:

1. **High-Frequency Ultrasound**: Useful for evaluating lesion thickness and detecting regional lymphadenopathy.12
2. **Positron Emission Tomography (PET)/Computed Tomography (CT)**: Critical for staging and identifying distant metastases in advanced cases.
3. **Magnetic Resonance Imaging (MRI)**: Especially valuable for evaluating subungual lesions or lesions near critical structures.12

Molecular and Genetic Testing

Molecular studies provide insights into the genetic alterations underlying ALM and may inform treatment strategies. Unlike other melanoma subtypes, ALM commonly exhibits mutations in the KIT gene, along with focal amplifications of cyclin D1 (CCND1) and loss of PTEN. These genetic features distinguish ALM from melanomas associated with BRAF or NRAS mutations.12

Fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) are increasingly employed to identify actionable genetic mutations. Molecular profiling is particularly important for guiding targeted therapies, such as KIT inhibitors, in patients with advanced disease.12

Staging and Prognostic Evaluation

Accurate staging is critical for guiding treatment. The American Joint Committee on Cancer (AJCC) staging system incorporates:

- **Tumor Thickness (Breslow Depth)**: Measured in millimeters; a key prognostic factor.
- **Ulceration**: Presence indicates a worse prognosis.12
- **Regional Lymph Node Involvement**: Assessed through sentinel lymph node biopsy (SLNB), which is recommended for lesions ≥1 mm in thickness or those with high-risk features.12
- **Distant Metastases**: Identified through imaging and clinical evaluation.12

Differential Diagnosis

The diagnostic process must consider several conditions that mimic ALM, including:

- Acral nevi (distinguished by benign dermoscopic patterns).12
- Subungual hematomas (characterized by a history of trauma and lack of Hutchinson's sign).
- Onychomycosis (confirmed through fungal culture).
- Plantar warts and calluses (absence of pigmentation and dermoscopic findings consistent with keratinization).13

The diagnosis of ALM requires a multimodal approach, integrating clinical, dermoscopic, histological, and molecular data. Early detection and accurate differentiation from benign mimics are paramount for improving outcomes. Advances in diagnostic imaging and molecular profiling hold promise for enhancing the precision and timeliness of ALM diagnosis, ultimately guiding tailored therapeutic interventions.14

Treatment

The management of acral lentiginous melanoma (ALM) is multifaceted and depends on the stage of disease at diagnosis, the lesion's anatomical location, and the patient's overall health status. ALM is often diagnosed at an advanced stage due to its subtle early clinical presentation and lack of awareness among patients and healthcare providers. Consequently, treatment frequently necessitates an aggressive, multidisciplinary approach that combines surgical, medical, and, in some cases, emerging therapeutic modalities.15

Surgical Management

Surgery remains the cornerstone of treatment for localized ALM, with the goal of achieving complete tumor resection while preserving function and cosmesis.15

1. **Wide Local Excision (WLE)**
    - WLE is the standard of care for primary ALM lesions. The surgical margin is determined by the Breslow depth of the tumor:
        - **In situ melanoma**: A margin of 0.5–1 cm.
        - **Tumors ≤1 mm in thickness**: A margin of 1 cm.
        - **Tumors >1 mm in thickness**: A margin of 1–2 cm.
    - Achieving clear margins is critical, as positive margins are associated with a higher risk of local recurrence. However, the unique anatomical constraints of acral sites often make achieving these margins challenging, necessitating careful surgical planning.15
2. **Subungual Lesions**
    - Subungual ALM often requires complete removal of the nail apparatus. In more advanced cases, amputation of the distal phalanx may be necessary to ensure complete tumor excision. Preservation of function and aesthetics is prioritized where possible, particularly in cases diagnosed early.15
3. **Sentinel Lymph Node Biopsy (SLNB)**
    - SLNB is indicated for patients with primary tumors ≥1 mm in thickness or those with high-risk features (e.g., ulceration, high mitotic rate).
    - Identification of sentinel lymph node involvement helps guide staging and subsequent treatment decisions.15
4. **Regional Lymphadenectomy**
    - If SLNB reveals metastasis, complete lymph node dissection may be recommended. However, the role of regional lymphadenectomy is being reevaluated in light of emerging evidence suggesting limited survival benefit in certain patients.15

Adjuvant Therapy

Adjuvant therapies are employed to reduce the risk of recurrence in patients with high-risk or locally advanced ALM.

1. **Immune Checkpoint Inhibitors**
    - **Anti-PD-1 Agents (e.g., Pembrolizumab, Nivolumab)**: These agents are commonly used as adjuvant therapy for patients with stage III or resected stage IV melanoma. They enhance the immune response against melanoma cells by inhibiting the programmed death-1 (PD-1) pathway.15
    - **CTLA-4 Inhibitors (e.g., Ipilimumab)**: While effective, these are less commonly used due to their higher toxicity compared to anti-PD-1 agents.15
2. **Targeted Therapy**
    - Unlike cutaneous melanomas, ALM rarely harbors BRAF mutations but may exhibit mutations in the KIT gene.15
    - **KIT Inhibitors (e.g., Imatinib, Dasatinib)**: In patients with KIT-mutant ALM, these agents have shown efficacy in reducing recurrence risk and controlling advanced disease.15

Systemic Therapy for Advanced Disease

For patients with metastatic or unresectable ALM, systemic therapies are the primary mode of treatment.

1. **Immunotherapy**
    - Checkpoint inhibitors, such as **anti-PD-1 agents** and **anti-CTLA-4 agents**, are first-line treatments for metastatic melanoma. These therapies have demonstrated durable responses in a subset of patients.15
    - **Combination Immunotherapy**: Combining anti-PD-1 and anti-CTLA-4 agents can improve response rates but is associated with increased toxicity.15
2. **Targeted Therapy**
    - In patients with actionable genetic mutations (e.g., KIT mutations), KIT inhibitors may be employed.15
    - While BRAF-targeted therapies (e.g., dabrafenib and trametinib) are standard for BRAF-mutant cutaneous melanomas, their role in ALM is limited due to the rarity of BRAF mutations in this subtype.15
3. **Cytotoxic Chemotherapy**
    - Traditional chemotherapeutic agents, such as dacarbazine or paclitaxel, have limited efficacy in melanoma but may be considered in select cases where other treatments are unavailable or ineffective.15
4. **Combination Therapies**
    - Combining immunotherapy and targeted therapy is being explored in clinical trials to overcome resistance and enhance efficacy in advanced ALM.15

Radiation Therapy

Radiation therapy is not a primary treatment modality for ALM but may be employed in specific situations:

- As an adjunct for palliative care to control symptoms in metastatic disease.
- To treat unresectable primary tumors or residual disease following surgery.
- For adjuvant treatment in patients with high-risk features, such as lymph node involvement.15

Emerging Therapies

1. **Oncolytic Viral Therapy**
    - Talimogene laherparepvec (T-VEC), an oncolytic virus engineered to selectively infect and destroy melanoma cells, is being evaluated in ALM.15
2. **Adoptive Cell Therapy**
    - Therapies such as tumor-infiltrating lymphocytes (TILs) or CAR-T cells offer a novel approach to enhance immune-mediated tumor destruction.15
3. **Photodynamic Therapy (PDT)**
    - Though still experimental, PDT may have a role in the management of early-stage ALM lesions.15

Palliative Care

In patients with advanced, incurable ALM, the focus shifts to symptom management and improving quality of life. Pain control, management of ulceration or infection, and psychosocial support are integral to palliative care.15

Multidisciplinary Approach

Given the complexities of ALM management, a multidisciplinary team—including dermatologists, oncologists, surgeons, pathologists, and palliative care specialists—is essential. Collaboration ensures that treatment plans are individualized, balancing disease control with preservation of function and quality of life.15

The treatment of ALM requires a nuanced and multimodal approach, reflecting its aggressive nature and frequent late-stage diagnosis. Advances in immunotherapy and targeted therapy have improved outcomes for many melanoma patients, but ALM's unique genetic and clinical characteristics necessitate further research to develop optimized treatment strategies. Early detection and awareness remain critical for improving survival rates and reducing the burden of this challenging melanoma subtype.15

CONCLUSION

Acral lentiginous melanoma (ALM) represents a unique and formidable challenge within the broader spectrum of melanomas. Its rarity, predilection for acral sites, and distinct clinical, dermoscopic, histopathologic, and molecular characteristics set it apart from other melanoma subtypes. Despite comprising a small proportion of melanoma cases globally, ALM is disproportionately represented in populations with darker skin tones, highlighting the interplay of biological, genetic, and social determinants in its diagnosis and management.

The delayed recognition of ALM, owing to its subtle presentation and resemblance to benign lesions, significantly contributes to its advanced stage at diagnosis and poorer prognosis compared to other melanomas. This underscores the critical need for increased awareness among healthcare providers and patients, particularly in high-risk populations. Dermoscopy and histopathological examination remain the diagnostic cornerstones, with advances in molecular profiling offering new avenues for precision medicine.

Surgical excision, tailored to tumor thickness and anatomical constraints, remains the foundation of treatment for localized disease. For advanced stages, the emergence of immunotherapy and targeted therapies has revolutionized melanoma management, although their efficacy in ALM is limited by the subtype's unique molecular profile. KIT mutations, more prevalent in ALM than in other melanomas, provide an opportunity for targeted therapy, but their overall frequency underscores the pressing need for research into novel therapeutic targets.

The multidisciplinary approach to ALM management is essential, integrating expertise from dermatology, oncology, pathology, surgery, and supportive care to ensure comprehensive and patient-centered care. This approach is particularly important given the complex interplay of functional and cosmetic considerations in treating acral and subungual lesions.

Future directions in ALM research must prioritize early detection strategies, such as public health campaigns and clinician training, to reduce diagnostic delays. Additionally, the development of more effective systemic therapies tailored to ALM's genetic and immunologic landscape holds promise for improving outcomes in advanced disease. Advances in molecular diagnostics, immunotherapy, and personalized medicine offer hope for addressing the current gaps in ALM care, ultimately reducing the disease burden.

In conclusion, ALM remains a significant clinical challenge, requiring concerted efforts in early detection, innovative therapeutic development, and equitable healthcare delivery. By fostering awareness and advancing research, it is possible to mitigate the disparities and improve the prognosis for patients affected by this rare but aggressive melanoma subtype.

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