The Misdiagnosis of Acral Lentiginous Melanoma

Three Case Presentations

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Acral lentiginous melanoma (ALM) is a disease that is found on the palms, soles, and nail beds. Because these areas are not often examined during general medical examinations, the presence of ALM often goes unnoticed or the diagnosis is delayed. Research shows that the misdiagnosis of ALM is common, reported between 20% and 34%. We present three cases of ALM that were initially misdiagnosed and referred to the senior author (B.C.M.) in an effort to assess why misdiagnosis is common. The existing literature illuminates clinical pitfalls in diagnosing ALM. The differential diagnosis of many different podiatric skin and nail disorders should include ALM. Although making the correct diagnosis is essential, the prognosis is affected by the duration of the disease and level of invasiveness. Unfortunately, most of the reported misdiagnosed cases are of a later stage and worse prognosis. This review highlights that foot and ankle specialists should meet suspect lesions with a heightened index of suspicion and perform biopsy when acral nonhealing wounds and/or lesions are nonresponsive to treatment. (J Am Podiatr Med Assoc 109(2): 166-171, 2019)

The American Cancer Society estimates that 87,110 new cases of melanoma will ultimately have been diagnosed in 2017 and 9,730 people will succumb to cutaneous melanomas.[1] Acral lentiginous melanoma accounts for 2% to 10% of all melanoma.[2-4] ALM has a poor prognosis because of location alone and often remains undetected for extended periods, as it presents on plantar and distal surfaces.[3] These lesions may also present deficient in pigment (ie, amelanotic variants lacking varying shades of tan/brown/black), which does not raise as much suspicion as would a deeply pigmented lesion.[5] This is thought to be one factor contributing to the delay in diagnosis and subsequent treatment.

While reviewing the literature, we found that the majority of reported cases involved white patients, and that three retrospective studies also had reported a majority of white patients.[3,6,7] However, the true incidence is similar among dark- and light-skinned individuals alike (reported as 1.8 per 1 million person-years).[4] Despite the incidence of ALM being similar, darker skinned people present with melanoma on the palms, soles, and nail beds more often when compared to other subtypes of melanoma.[8] This is important to remember when forming a differential diagnosis, because ALM is not directly related to sun exposure as is the case with other subtypes.[9]

Reports illustrate the commonality of misdiagnosing this disease. Between 20% and 34% of ALM cases are initially misdiagnosed, causing a delay in treatment.[2,6,7,10] It is generally accepted that early recognition and diagnosis has a better outcome. Prognosis of cutaneous melanoma is predominantly determined by tumor depth at the time of diagnosis. In a report by Albreski and Sloan, 48% of the

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reviewed cases were of Clark level IV/V at the time of correct diagnosis, indicating poor prognosis.[3] Intuitively, this delay in diagnosis and treatment could allow for progression of the lesion, although there is no true way of telling the lesion progressed between the incorrect diagnosis and the correct diagnosis.

Albreski and Sloan also found that 77% of the reviewed cases were on the lower extremity.[3] A wide variety of possible podiatric diagnoses should include ALM in the differential diagnosis: verruca, callous/corn, tinea pedis, foreign body, eccrine poroma, nevus, subungual hematoma, pyogenic granuloma, onychomycosis, onychocryptosis, diabetic foot ulcer, and tumors (Table 1).[3,5,10,11,12] Reports are also found involving interdigital maceration, patient-reported trauma, and amelanotic variants, highlighting the real possibility of mistaking ALM lesions for more benign diagnoses (Table 2).[12-14] We present three cases that were initially misdiagnosed and treated before being referred to the senior author (B.C.M.) for further evaluation and biopsy, leading to the true diagnosis of acral lentiginous melanoma.

Table 1. Misdiagnoses of ALM Found in the Literature

Subungual lesions
Onychomycosis
Onychocryptosis
Subungual hematoma
Paronychia
Sole lesions
Verruca plantaris
Eccrine poroma
Keratoacanthoma
Mal perforans
Callous/corn
Nonhealing ulcer
Varying locations
Trauma
Pyogenic granuloma
Blister
Nevus
Tumors
Foreign body
Gangrene

Case Series

Case 1

A 50-year-old man sustained trauma to the hallux 2 years before referral to the senior author (Fig. 1). The patient regarded the appearance of the toe to be a direct result of the trauma. On presentation, the nail appeared darkened, as in a subungual hematoma. Because of the duration of symptoms and the uncertainty of the etiology, a biopsy was performed. The biopsy results revealed ulcerated epidermis with evident pleomorphic epithelioid cells containing large amounts of melanin pigment on low magnification (Fig. 2) and dermal mitotic figures on high magnification (Fig. 3). These findings led to the diagnosis of ALM.



Figure 1. A case of acral lentiginous melanoma following nail debridement that was misdiagnosed as subungual hematoma.

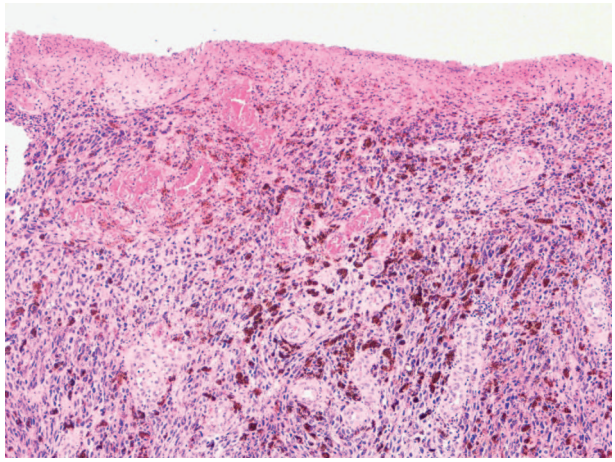


Figure 2. The epidermis is ulcerated, with a subjacent tumor composed of large pleomorphic epithelioid cells containing large amounts of melanin pigment (×10).

Table 2. Case Reports Found Through Literature Review Including Gathered Metrics

Initial Diagnosis	Age (yr)	Sex	Ethnicity/ Race[a]	Location	Tumor Thickness (mm)	Metastasis	Delay in Treatment[b]	Authors
Tinea pedis	68	M	Turkish white	Interdigital	18	Inguinal lymph nodes	1 yr	Serarslan et al
Verruca plantaris	42	F	Scandinavian white	Plantar midfoot	30	Bone and pulmonary lymph nodes	1 yr	Rosen
Verruca plantaris	69	F	White	Plantar heel	1.31	Hilar and mediastinal lymph nodes	4 yr	Chokoeva et al
Trauma	66	F	White	Plantar heel	3.15	Popliteal lymph nodes with lymphovascular involvement	2 mo	Gumaste et al
DFU	87	F	Slavic	Subungual	10–20	Inguinal lymph nodes	2 yr	Mansur et al
DFU	52	F	Malay	Plantar midfoot	5.5	No metastasis	4 mo	Hussin et al
DFU	61	M	White	Medial aspect of hallux	NA	Sentinel and pulmonary lymph nodes with vascular, cartilaginous, and osseous tissue invasion	NA	Albreski and Sloan[c]

Abbreviations: M, male; F, female; DFU, diabetic foot ulcer; NA, not applicable.
[a]Ethnicity and/or race reported when available.
[b]Delay in treatment defined as time between initial diagnosis and diagnosis of ALM.
[c]Albreski and Sloan included in this table based on their description of an "exemplary case report."

Case 2

A 52-year-old man was treated for paronychia for 4.5 months with chronic drainage and lysis of the right hallucal nail. The lesion on initial presentation was amelanotic; however, on later examination, the patient was uncertain about the duration of multiple adjacent pigmented streaks also present in the nail plate (Fig. 4). Because of nonresolution of diagnosed infection and the onset of suspicious hyperpigmentation, the patient was referred to the senior author for a second opinion. Immediate nail-bed biopsy revealed deeply invasive ALM. On histologic examination, there was evidence of lentiginous proliferation of solitary melanocytes along the basal layer of the epidermis with scattered nests (Fig. 5), and tumor cells could be found extending deep into the dermis (Fig. 6). The patient was found to have positive sentinel lymph nodes on biopsy, and later found to have metastases to the lung. The patient enrolled in a clinical trial for targeted molecular chemotherapy.

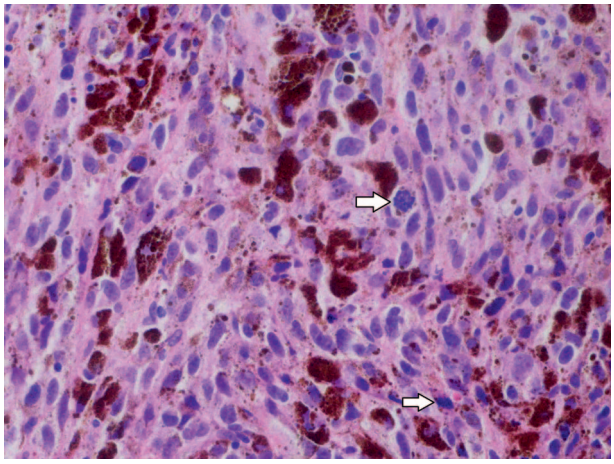


Figure 3. High magnification (×40) reveals two dermal mitotic figures (arrows).



Figure 4. A case of acral lentiginous melanoma misdiagnosed as chronic paronychia. Melanonychia striata evident and Hutchinson's sign found on proximal nail fold.

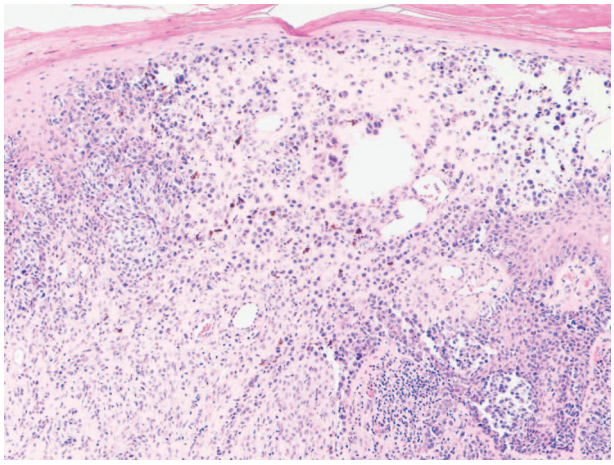


Figure 5. There is a confluent lentiginous proliferation of solitary melanocytes along the basal layer of the epidermis with scattered nests. The cells are large and pleomorphic and extend deep into the dermis. Scattered melanin pigment is present (×10).

Case 3

A 64-year-old man was treated for onychomycosis with chronic subungual bleeding. It was presumed for several months that the subungual bleeding was caused by shoe trauma to the patient's thickened and dystrophic nail (Fig. 7). Based on the senior author's suspicion that the discoloration was attributable to pigment, a biopsy was performed. The results of the biopsy revealed a high density of large pleomorphic melanocytes along the basal layer of the epidermis (Fig. 8). A sentinel lymph node biopsy was obtained, and Melan-A immunohistochemical staining revealed metastatic melanoma cells within the lymph node peripheral sinus and in the lymph node parenchyma (Fig. 9).

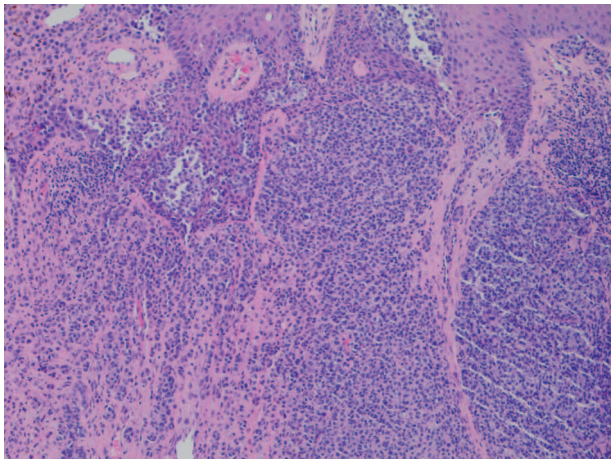


Figure 6. As the tumor cells descend into the dermis, there is little to no maturation (×10).



Figure 7. A case of acral lentiginous melanoma initially diagnosed as recalcitrant onychomycosis with subungual bleeding.

Discussion

A history of trauma often leads clinicians astray. Patient-reported incidents should be met with a heightened index of suspicion such as in the first case. Albreski and Sloan reported 40% of the lower

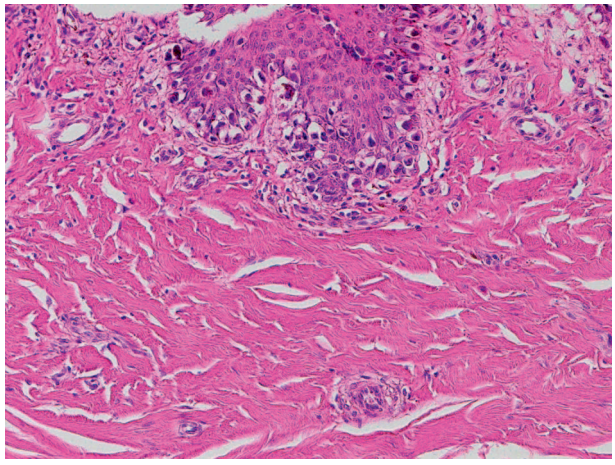


Figure 8. There is a high density of large pleomorphic melanocytes along the basal layer of the epidermis with small clusters and solitary cells within the dermis (×20).

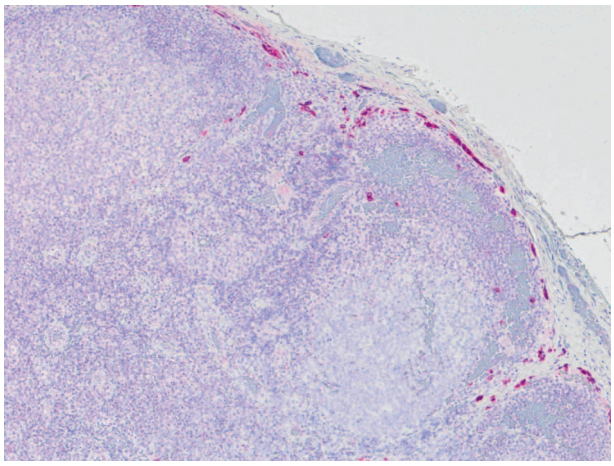


Figure 9. Melan-A immunohistochemical stain reveals metastatic melanoma cells within the lymph node peripheral sinus, and within the lymph node parenchyma (×10).

extremity misdiagnoses to be trauma.[3] It is probable that patients will know why they attained an acute lesion, but spreading or persistent lesions warrant further examination and an expanded differential diagnosis. Because subungual hematomas resolve quicker than the duration of this patient's symptoms, a biopsy was warranted to further assess the etiology of the hard-to-heal lesion.

One should also keep in mind when dealing with patient-reported trauma (and other suspicious lesions in general) patient/family medical history. Gumaste et al reported a similar misdiagnosed case of nonhealing patient-reported trauma in which the patient history included melanoma of the arm and the family history included melanoma and other cancers.[12] Patient and family history of cancers (not just melanoma) can aid in justifying a biopsy.

The second case presents two difficult problems: 1) it was disguised as chronic paronychia, and 2) the lesion was amelanotic on first examination. Infections are commonplace in the podiatric setting so it is easy to become complacent when evaluating and treating them. Albreski and Sloan report that 34% of the reviewed cases were treated first as an infection.[3] Any infection that is nonresponsive to standard-of-care treatment should have the lesion and the differential diagnosis reevaluated.

Amelanotic variants of ALM are concerning regarding the dismissal of pigmented differential diagnoses and the number of misdiagnosed cases. Soon et al report that of 53 cases misdiagnosed, nearly half were amelanotic at presentation.[7] For the second patient, it was not until the appearance of melanonychia striata in the nail plate and Hutchinson's sign on the medial aspect of the proximal nail fold that suspicion was raised (Fig. 4). Even pigmented streaks within the nail plate can be misleading because of the commonality of the appearance. Melanonychia striata is common in darker pigmented individuals and has been reported to occur in as many as 77% to 100% of individuals older than 50 years.[15] Clinicians should monitor nail/nail-fold pigmentation for change and evolution and note the patient/family history of cancers. A biopsy of the nail bed should be performed when firm clinical grounds warrant doing so.

Onychomycosis is one of the most common diagnoses that podiatrists treat. The commonality, paired with the recalcitrance of most fungal nail infections to treatment, can often lead to a long and monotonous duration of constant treatment. Discoloration is also common, with fungal nail infections masking hyperpigmentation or causing clinicians to dismiss pigmented differential diagnoses. Nail dystrophy and shoe trauma can lead to subungual bleeding, which may appear like hyperpigmentation. Nonresolution of the subungual hematoma after proper nail debridement and possible shoe modification should raise flags as to the etiology of the pigmentation. The third patient is an example of how pigmentation can be mistaken for discoloration/trauma. It is important to order the proper laboratory tests (eg, potassium hydroxide preparation, fungal cultures) to confirm clinical diagnoses, and to perform biopsy when necessary.

Conclusions

Acral lentiginous melanoma is a challenging diagnosis because of propensity to be misdiagnosed as other common podiatric diseases. Location alone is directly linked to a poorer prognosis.[2] If the treatment is delayed, the depth of the lesion may increase, increasing the chance of metastasis. Nearly all of the misdiagnosed cases in the literature were advanced and invasive melanomas with poor prognoses.

Lesions that are nonresponding for longer than expected, patient-reported trauma, patient and/or family history of melanoma and nonmelanoma skin cancers, and nonhealing wounds should all be met with a heightened index of suspicion. Biopsy remains the most effective method of determining the true nature of a lesion. This review demonstrates that foot and ankle specialists should perform thorough skin examinations, note the

presence of skin and nail lesions (especially when not the chief complaint), and perform biopsies on firm clinical grounds for suspect lesions.

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