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National Comprehensive Analysis of Characteristics of Acral Lentiginous Melanoma

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Abstract. *Background/Aim: Acral lentiginous melanoma (ALM) is the least common subtype of cutaneous melanoma and typically occurs on the palms, soles, and nails. Tumor characteristics and disease severity in the US population are not well understood. Our aim was to analyze the characteristics of ALM of the extremities. Patients and Methods: We queried the National Cancer Database to identify patients with the diagnosis of ALM and common malignant melanoma located in the extremities (CMME). We compared demographic, tumor, and treatment characteristics between patients with ALM and those with CMME. Statistical analysis was performed with chi-squared test and multivariate logistic regression models. Results: We identified 5,203 patients with ALM and 118,485 with CMME. When compared with patients with CMME, those with ALM were more likely to be older than 80. years at diagnosis [odds ratio (OR)=2.85, 95% confidence intervaI (CI)=2.12-3.82; p<0.001], have stage III disease (OR=4.22, 95% CI=1.47-12.16; p=0.01), and have ulceration (OR=1.52, 95% CI=1.33-1.74; p<0.001). Moreover, patients with ALM were less likely to have a mitotic count of 1/mm^2 or greater (OR=0.57, 95% CI=0.48-0.67; p<0.001). No statistical difference was found for sex, lymph node involvement, regression, and use of surgery, radiotherapy, and immunotherapy between groups. Conclusion: Age, disease stage, ulceration, and mitotic count are independent factors associated with ALM. Knowledge of the disease characteristics may allow for better diagnosis and understanding of disease pathophysiology.*

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Acral lentiginous melanoma (ALM) is the rarest melanoma subtype with worst prognosis in the United States, accounting for approximately 1% to 7% of all melanomas in White persons (1). ALM primarily affects the glabrous skin of the palms and soles, including the nails of the upper and lower extremities (2). It is characterized by proliferation of atypical melanocytes in the dermoepidermal junctions and extension into deeper structures when invasive (3).

ALM is challenging to diagnose with the classic ABCDE criteria (asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolving characteristics). The pigmentation of a benign melanocytic nevus located in an acral site extends along the skin markings of the palms and soles, therefore mimicking malignant lesions (1). Moreover, an ALM lesion can be technically difficult to biopsy because of its location (2).

Regarding prognostic factors, only age, ulceration and tumor thickness were found to be associated with ALM in Brazilian and German patients (4). Improved understanding of the prognostic factors of ALM in the US population will allow healthcare providers to determine the disease status and improve management. The aims of this study were to analyze the characteristics of ALM and to compare them with those of common malignant melanoma located in the extremities (CMME).

Patients and Methods

We performed a retrospective analysis of ALM and CMME cases that were registered in the National Cancer Database (NCDB) from January 1, 2004, through December 31, 2015. We included patients with a confirmed histopathological diagnosis of ALM or CMME. Although CMME was classified as melanoma of the extremities with the histologic characteristics of "malignant melanoma not otherwise specified", this definition included patients with melanoma not specified at diagnosis and located in the upper and lower extremities. Patients with melanoma classified as other histological types or located in sites other than the extremities were

Table I. *Demographics and tumor characteristics*.

		ALM (N=5,203), n (%)	CMME (N=118,485), n (%)	*p*-Value
Age group	<40 Years	350 (6.7%)	14,153 (11.9%)	**<0.001**
	40-60 Years	1,640 (31.5%)	44,995 (38%)	
	61-80 Years	2,371 (45.6%)	47,347 (40%)	
	>80 Years	842 (16.2%)	11,990 (10.1%)	
Gender	Male	2,347 (45.1%)	49,071 (41.4%)	**<0.001**
	Female	2,856 (54.9%)	69,414 (58.6%)	
Race	White	4,368 (84%)	114,545 (96.7%)	**<0.001**
	Black	532 (10.2%)	1,078 (0.9%)	
	Native American	24 (0.5%)	110 (0.1%)	
	Asian	147 (2.8%)	451 (0.4%)	
	Other	61 (1.2%)	487 (0.4%)	
	Unknown	71 (1.4%)	1,814 (1.5%)	
Stage	0	375 (7.2%)	36,141 (30.5%)	**<0.001**
	I	1,905 (36.6%)	48,636 (41%)	
	II	1,348 (25.9%)	12,228 (10.3%)	
	III	1,162 (22.3%)	8,108 (6.8%)	
	IV	104 (2%)	1,809 (1.5%)	
	Unknown	309 (5.9%)	11,563 (9.8%)	
Breslow depth	≤1 mm	1,682 (32.3%)	46,276 (39.1%)	**<0.001**
	1.01-2 mm	1,050 (202%)	15,415 (13%)	
	2.01-4mm	1,018 (19.6%)	8,460 (7.1%)	
	>4 mm	878 (16.9%)	5,298 (4.5%)	
	Unknown	575 (11.1%)	43,036 (36.3%)	
Ulceration	No ulceration	3,156 (607%)	89,832 (75.8%)	**<0.001**
	Ulceration present	1,730 (33.3%)	13,088 (11%)	
	Unknown	317 (6.1%)	15,565 (13.1%)	
Mitotic count	No mitoses	644 (12.4%)	15,068 (12.7%)	**<0.001**
	<1/mm^2	204 (3.9%)	3,271 (2.8%)	
	≥1/mm^2	1,699 (32.7%)	17,827 (15%)	
	Unknown	2,656 (51%)	82,319 (69.5%)	
	Negative	1,202 (23.1%)	38,761 (32.7%)	
Lymph nodes	Positive	3,433 (66%)	8,713 (7.4%)	0.06
	Unknown	1,770 (34%)	71,011 (59.9%)	
	No	2,119 (407%)	36,912 (31.2%)	
Regression	Yes	248 (4.8%)	3,782 (3.2%)	
	Unknown	2,836 (54.5%)	77,791 (65.7%)	
Surgery	No	56 (1.1%)	1,678 (1.4%)	**0.04**
	Yes	5,139 (98.8%)	116,608 (98.4%)	
	Unknown	8 (02%)	199 (0.2%)	
Radiation	No	5,065 (97.3%)	116,224 (98.1%)	**<0.001**
	Yes	100 (1.9%)	1,373 (1.2%)	
	Unknown	38 (07%)	888 (0.7%)	
Immunotherapy	No	4,772 (91.7%)	114,413 (96.6%)	**<0.001**
	Yes	362 (7%)	2,856 (2.4%)	
	Unknown	69 (1.3%)	1,216 (1%)	

ALM: Acral lentiginous melanoma; CMME: common malignant melanoma of the extremities. Bold values indicate statistical significance.

excluded from the study. Patients with missing data were also excluded from the analysis.

Statistical analysis. We compared demographic and tumor characteristics by using the chi-squared test. After adjustment for age and sex, multivariate logistic regression was performed to compare the risks of tumor characteristics in patients with ALM with those with CMME. Odds ratios (ORs) and confidence intervaIs (CIs) were calculated to compare the groups, and $p<0.05$ was considered statistically significant. All analyses were performed with SPSS software version 25 (IBM, Armonk, NY, USA).

Results

A total of 5,203 patients had ALM, and 118,485 had CMME. Mean age (±SD) at diagnosis of ALM was 64.3 ± 15.41 years. Most patients were White (84%) and women (54.9%),

and almost half were between 61 and 80 years old (45.6%) (Table I). The most common severity of ALM was stage I (36.6%). Common tumor characteristics included Breslow depth of 1 mm or less (32.3%), absence of ulceration (60.7%), mitotic count of 1/mm^2 or greater (32.7%), positive lymph node status (66%), and absence of regression (40.7%). In addition, 98.8% of patients with ALM underwent surgical procedures, without radiotherapy (97.3%) or immunotherapy (91.7%) (Table I).

Compared with those with CMME, patients with ALM were more likely to be older than 80 years at diagnosis (OR=2.85, 95% CI=2.12-3.82; $p<0.001$), have stage III disease (OR=4.22, 95% CI=1.47-12.16; $p=0.01$), and have ulceration (OR=1.52, 95% CI=1.33-1.74; $p<0.001$). However, compared with patients with CMME, those with ALM were less likely to have a mitotic count of 1/mm^2 or greater (OR=0.57, 95% CI=0.48-0.67; $p<0.001$). No statistical difference was found for sex, lymph node involvement, regression, and use of surgery, radiotherapy, and immunotherapy between groups (Table II).

Table II. *Multivariate analysis of characteristics of acral lentiginous melanoma compared with common malignant melanoma of the extremities.*

	Multivariate analysis		
Variable	OR*	95% CI	*p*-Value
Age group			
<40 Years	1.00	-	-
40-60 Years	2.25	1.74-2.92	<0.001
61-80 Years	2.65	2.05-3.43	<0.001
>80 Years	2.85	2.12-3.82	<0.001
Gender			
Male	1.00	-	-
Female	1.09	0.97-1.22	0.14
Stage			
0	1.00	-	
I	2.33	0.85-6.36	0.10
II	2.72	0.99-7.47	0.05
III	4.22	1.47-12.16	0.01
IV	3.23	1.04-10.09	0.04
Breslow depth			
≤1 mm	1.00	-	-
1.01-2 mm	1.49	1.27-1.76	<0.001
2.01-4 mm	2.17	1.76-2.68	<0.001
>4 mm	2.53	2.03-3.15	<0.001
Ulceration			
No	1.00	-	-
Yes	1.52	1.33-1.74	<0.001
Mitotic count			
No mitosis present	1.00	-	-
<1/mm^2	0.87	0.67-1.13	0.30
≥1/mm^2	0.57	0.48-0.67	<0.001
Lymph nodes involvement			
Negative	1.00	-	-
Positive	1.20	0.85-1.70	0.30
Regression			
No	1.00	-	-
Yes	0.98	0.81-1.18	0.82
Surgery			
No	1.00	-	-
Yes	1.10	0.32-3.79	0.88
Radiation			
No	1.00	-	-
Yes	0.71	0.48-1.04	0.08
Immunotherapy			
No	1.00	-	-
Yes	1.01	0.81-1.26	0.95

OR: Odds ratio; CI: confidence interval. *Only ORs associated with a CI not crossing 1.0. are shown.

Discussion

To our knowledge, this study analyzed the largest number of patients with ALM (n=5,203) in the United States. In 1976, Reed defined ALM for the first time as pigmented lesions on the extremities, particularly on the palms and soles, characterized by a radial (*i.e.*, lentiginous) growth pattern that evolves over months or years to a vertical invasive stage (5). Classic risk factors for melanoma, including sun exposure, fair skin, and preexisting melanocytic nevi, do not seem to apply to ALM (6). Previous trauma (6), pressure (7), and distinct genomic mutations (8) may promote the development of ALM. Compared with other subtypes, ALM has the worst prognosis because of its inherent biological behavior and the difficulty in identifying lesions (9). Melanocytes in acral skin lack hair follicles; therefore, they do not contain melanocytic stem cells and are more susceptible to replicative stress and genomic aberrations (2). Knowledge of clinical factors is useful for clinical suspicion and diagnosis of melanotic lesions in acral areas. Previous studies have shown that being male (6), and having a more advanced pathological stage (10, 11), greater Breslow thickness (12), the presence of ulceration (12), more than 15 mitoses/mm^2 (11), and sentinel lymph node positivity (12) are independent prognostic factors for patients with ALM.

In our study, more than one-half of all patients with ALM received the diagnosis of stage II disease or greater. In addition, almost one-third had a Breslow depth greater than 1 mm, ulceration, and a mitotic count of 1/mm^2 or greater. These findings suggest that many patients had advanced disease at the time of diagnosis and thus had a higher risk of death. Lino-Silva *et al*. analyzed the characteristics of 715 patients with ALM and reported that the 5-year disease-specific survival decreased as disease stage increased: 53.5% for patients with stage I ALM, 52.7% for those with stage II, and 40.8% for those with stage III (13). Bradford *et al*. reported similar results for 10-year survival, and they reported that patients with ALM had a 10.% to 15% lower survival rate than patients with CMM (10). Patients

diagnosed with ALM were also more likely to be older; this was most likely attributable to misdiagnosis, which occurs in approximately 40.% of patients (14).

We found a high percentage of patients with ALM (66%) had a positive sentinel lymph node at diagnosis, although this was not a factor associated with ALM. These findings highlight the importance of performing lymph node biopsy during initial management and serial physical examinations during follow-up. In a series of 281 patients, Bello *et al*. demonstrated that a more advanced disease stage, the presence of ulceration, a greater Breslow thickness, and a positive sentinel lymph node were prognostic factors associated with poor survival, and patients with ALM had worse survival than patients with nonacral cutaneous melanoma (12). Ulcerations in patients with CMM were related to a biological phenomenon resulting from proliferative cell activity and overexpression of c-MYC; in comparison, ALM may be related to previous trauma (15).

Interestingly, patients with ALM had a lower likelihood of having a mitotic count of 1/mm^2 or greater. Although whether the mitotic count is a prognostic factor for patients with ALM remains controversial, our results are consistent with those of other studies that did not find any statistical difference in the association with survival (12, 16). In contrast, Lv *et al*. identified a higher mitotic rate of greater than 15/mm^2 as an independent prognostic factor for ALM (11). These differences may be related to variance in the mitotic rates calculated in these studies.

This study has limitations. We collected data from the NCDB, and thus our results were limited by the accuracy of data provided nationally. To obtain the most reliable results, we excluded patients with missing data, which might have affected the models. Furthermore, the NCDB likely misrepresents ALM owing to under-reporting by health care providers and hospitals. However, we are reassured that the results obtained from this study are concordant with those of similar studies.

Conclusion

We determined that being older, with a more advanced disease stage, a greater Breslow depth, presence of ulceration, and absence of mitosis are factors independently associated with ALM compared with CMME. Knowledge of these factors may help improve the diagnosis and treatment of this aggressive cancer. Nevertheless, further prospective studies are needed to better understand the pathophysiology and other potential risk factors of ALM.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

MTH, DJR and AJF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MTH, AJF, SPB, ACS. Acquisition, analysis, or interpretation of data: ACS, MTH, AJF. Drafting of the article: MTH, DJR, DB, RAV. Critical revision of the article for important intellectual content: SPB, ACS, BDR and AJF. Study supervision: BDR, AJF

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References

1 Nakamura Y and Fujisawa Y: Diagnosis and management of acral lentiginous melanoma. Curr Treat Options Oncol *19(8)*: 42, 2018. PMID: 29951919. DOI: 10.1007/s11864-018-0560-y

2 Whiteman DC, Pavan WJ and Bastian BC: The melanomas: A synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res *24(5)*: 879-897, 2011. PMID: 21707960. DOI: 10.1111/j.1755-148X.2011.00880.x

3 Hafliger EM, Ramelyte E, Mangana J, Kunz M, Kazakov DV, Dummer R and Cheng PF: Metastatic acral lentiginous melanoma in a tertiary referral center in Switzerland: A systematic analysis. Melanoma Res *28(5)*: 442-450, 2018. PMID: 29847461. DOI: 10.1097/cmr.0000000000000465

4 Nunes LF, Quintella Mendes GL and Koifman RJ: Acral melanoma: A retrospective cohort from the brazilian national cancer institute (inca). Melanoma Res *28(5)*: 458-464, 2018. PMID: 30020197. DOI: 10.1097/cmr.0000000000000476

5 Reed RJ: New Concepts in Surgical Pathology of the Skin. John Wiley & Sons, 1976.

6 Phan A, Touzet S, Dalle S, Ronger-Savle S, Balme B and Thomas L: Acral lentiginous melanoma: A clinicoprognostic study of 126 cases. Br J Dermatol *155(3)*: 561-569, 2006. PMID: 16911282. DOI: 10.1111/j.1365-2133.2006.07368.x

7 Minagawa A, Omodaka T and Okuyama R: Melanomas and mechanical stress points on the plantar surface of the foot. N Engl J Med *374(24)*: 2404-2406, 2016. PMID: 27305207. DOI: 10.1056/NEJMc1512354

8 Furney SJ, Turajlic S, Stamp G, Thomas JM, Hayes A, Strauss D, Gavrielides M, Xing W, Gore M, Larkin J and Marais R: The mutational burden of acral melanoma revealed by whole-genome sequencing and comparative analysis. Pigment Cell Melanoma Res *27(5)*: 835-838, 2014. PMID: 24913711. DOI: 10.1111/pcmr.12279

9 Piliang MP: Acral lentiginous melanoma. Clin Lab Med *31(2)*: 281-288, 2011. PMID: 21549241. DOI: 10.1016/j.cll.2011.03.005

10 Bradford PT, Goldstein AM, McMaster ML and Tucker MA: Acral lentiginous melanoma: Incidence and survival patterns in the United States, 1986-2005. Arch Dermatol *145(4)*: 427-434, 2009. PMID: 19380664. DOI: 10.1001/archdermatol.2008.609

11 Lv J, Dai B, Kong Y, Shen X and Kong J: Acral melanoma in Chinese: A clinicopathological and prognostic study of 142

cases. Sci Rep *6*: 31432, 2016. PMID: 27545198. DOI: 10.1038/srep31432
12 Bello DM, Chou JF, Panageas KS, Brady MS, Coit DG, Carvajal RD and Ariyan CE: Prognosis of acral melanoma: A series of 281 patients. Ann Surg Oncol *20(11)*: 3618-3625, 2013. PMID: 23838913. DOI: 10.1245/s10434-013-3089-0
13 Lino-Silva LS, Zepeda-Najar C, Salcedo-Hernandez RA and Martinez-Said H: Acral lentiginous melanoma: Survival analysis of 715 cases. J Cutan Med Surg *23(1)*: 38-43, 2019. PMID: 30221995. DOI: 10.1177/1203475418800943
14 Albreski D and Sloan SB: Melanoma of the feet: Misdiagnosed and misunderstood. Clin Dermatol *27(6)*: 556-563, 2009. PMID: 19880043. DOI: 10.1016/j.clindermatol.2008.09.014
15 Zhang N, Wang L, Zhu GN, Sun DJ, He H, Luan Q, Liu L, Hao F, Li CY and Gao TW: The association between trauma and melanoma in the Chinese population: A retrospective study. J Eur Acad Dermatol Venereol *28(5)*: 597-603, 2014. PMID: 23465057. DOI: 10.1111/jdv.12141
16 Jung HJ, Kweon SS, Lee JB, Lee SC and Yun SJ: A clinicopathologic analysis of 177 acral melanomaS IN KOREANS: RElevance of spreading pattern and physical stress. JAMA Dermatol *149(11)*: 1281-1288, 2013. PMID: 24067997. DOI: 10.1001/jamadermatol.2013.5853

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