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Review Article

Trauma could as a triggering factor for development of acral lentiginous melanoma: a clinicopathologic study of 56 cases

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Abstract: Background: The knowledge about Acral Lentiginous Melanoma's clinical presentation and histopathologic characteristics in East Asians is limited. Moreover, the association between trauma and melanoma has been a controversial issue. Methods: In order to assess clinical and pathological characteristics associated with melanoma, 56 Chinese patients with a trauma history have been investigated. The patients' demographic data and pathological observation has been studied. Statistical analyses including survival and univariate analyses of factor associated with survival were respectively performed by Kaplan-Meier method and the related analysis with traumatic events in acral lentiginous melanoma. Results: Post-trauma melanoma refers to melanoma occurring after trauma to the primary anatomic site. Our data collected from the two groups shows that it is statistically significant ($P < 0.05$) with age, cellular morphology and ulceration. Among the 56 acral lentiginous melanoma patients, the detailed descriptions of the anatomic sites of primary lesions were noted which included the nails of the thumbs and toes (13, 23.3%), the heels and plantar of the feet (39, 69.6%, 21 on the right, 18 on the left) and other sites (4, 7.1%). The prognosis of acral lentiginous melanoma was described to be significantly better with post-trauma melanoma than trauma-unrelated melanoma. Conclusions: Our findings provide epidemiological evidence for a potential association between traumatic events and acral lentiginous melanoma. In addition to genetic factors, trauma may also contribute to the development of melanoma with its influence on vasculogenisis and inflammation.

Keywords: Acral lentiginous melanoma, clinicopathologic study, inflammation, trauma

Introduction

Acral lentiginous melanoma (ALM) is a melanoma with poor prognosis which is frequently diagnosed at an advanced stage. Although the incidence of melanoma remains low in China, it has been increasing rapidly, with nearly 20,000 new cases reported each year. Acral lentiginous melanoma has become one of the diseases that poses a major threat to the health of Chinese people. The majority of cases of melanoma in Chinese population occur on the extremities, namely the hands and feet, it shows less correlation with sun exposure [1] and in these anatomic locations, post trauma melanoma (PTM) was more commonly found. Whether trauma could induce melanoma or not in the Caucasian population has been a controversial issue which has been debated in the literature since 1913. The association between trauma and melanoma has been controversial, since it is argued that the role of trauma in the development and progression of melanoma has been speculative. The purpose of this observational study was to investigate the potential association between traumatic events and ALM.

Materials and methods

Setting

From August 2003 to September 2015, 56 cases of ALM were collected from the De-

Table 1. Clinical characteristics of patients in post trauma melanoma and nonrelated trauma melanoma

Characteristics	Post-trauma melanoma No. (%) (n=12)	Trauma unrelated melanoma No. (%) (n=44)	*P*-value*
Age at diagnosis (years)			
≤ 65	2 (16.7)	23 (52.3)	0.028
> 65	10 (83.3)	21 (47.7)	
Gender			
Male	10 (83.3)	26 (59.1)	0.120
Female	2 (16.7)	18 (40.9)	
Localization			
Hands	3 (25.0)	3 (6.8)	0.071
Feet	9 (75.0)	41 (93.2)	

*Categorical variables were compared using Chi-square test.

partment of Dermatology at the First Affiliated Hospital of Wenzhou Medical University in Eastern China, standard medical records of the ALM were completed by two dermatologists which included name, gender, age, lesion location, detailed descriptions of history with trauma and the evolutionary process of the lesions.

Patient information

For each patient, the relationship between trauma and melanoma site was confirmed by the patient himself/herself. Patients who reported an ambiguous relationship between trauma and melanoma site were not considered suffering from PTM. Meanwhile, the pathological observations were evaluated by two board-certified dermatopathologists independently from our pathology department using the existing Hematoxylin-eosin (H&E) slides from routine diagnostics.

Statistical analysis

Chi-square test, Fisher's exact test and Kruskal-Wallis test for correlation detection of disease and the studied data, including gender, age, tumor's Breslow thickness, localization, chronic sun-induced damage (UV induced changes such as solar elastosis in the papillary dermis of the skin), ulceration, mitotic rate, infiltration of inflammatory cells, pathology stage, pigmentation and cytological types (**Tables 1**, **2**). Kaplan-Meier's test were performed in order to investigate statistically significant correlations between patients with PTM and trauma unrelated melanoma (TUM) in prognosis. The duration of overall survival (OS) was calculated from the pathologic diagnosis of melanoma till death or till the date of the last follow-up visit for patients who are still alive.

Results

PTM refers to melanoma occurring after trauma to the primary anatomic site (**Figure 1**). Among the 56 cases, there were 36 (64.3%) male and 20 (35.7%) female, with a male/female ratio of 1.8:1, all of whom were Chinese. Our data collected from the two groups show that it is statistically significant ($P < 0.05$) with age, cellular morphology and ulceration. In the PTM, patients were older, had more ulceration and their cellular morphology belonged to Spindle cells ($P < 0.05$). Male were significantly higher ($P < 0.05$) compared to female patients who recalled trauma in the group of PTM. Among the 56 ALM patients, the detailed descriptions of the anatomic sites of primary lesions were noted which included the nails of the thumbs and toes (13, 23.3%), the heels and plantar of the feet (39, 69.6%, 21 on the right, 18 on the left) and other sites (4, 7.1%). Most of the ALM occurred in the affected location (36 male, 20 female) and the traumatic events were more frequent on the feet than on the hands. In our series, the median follow-up was 26 months (range 3-148 months). The ALM-specific 5-year survival rate was 66.7%. 13 (23.3%) died due to evolution of their melanoma and in 2 (3.57%) patients the cause of death was not related to melanoma. Currently, 35 (62.5%) are still alive without evidence of residual disease and 6 (10.7%) patients are alive after recurrence. The duration of overall survival (OS) of 56 ALM patients - was significantly different between the patients with trauma and without trauma, the prognosis of ALM was described to be significantly better with PTM than TUM (**Figure 2**).

Discussion

ALM is a rare subtype of melanoma mainly arising on the nailbeds, the heels and plantar of the feet, it is most commonly found in Asia or Africa [2]. ALM was first defined in 1976 (3-5) and it

Table 2. Pathologic characteristics of patients in post trauma melanoma and nonrelated trauma melanoma

Factors	Post trauma melanoma No. (%) (n=12)	Trauma unrelated melanoma No. (%) (n=44)	*P*-value*
Histological type†			
NM	7 (58.3)	29 (69.0)	0.370
SSM	3 (25.0)	4 (9.5)	
ALM	2 (16.7)	9 (21.4)	
Ulceration			
With	11 (91.7)	23 (52.3)	0.013
Without	1 (8.3)	21 (47.7)	
Breslow thickness (mm)			
≤ 1 mm	0 (0.0)	3 (6.8)	0.881
1-4 mm	6 (50.0)	18 (40.9)	
> 4 mm	6 (50.0)	23 (52.3)	
Mitotic rate (mm^2)			
< 1	10 (83.3)	38 (86.4)	0.790
≥ 1	2 (16.7)	6 (13.6)	
Inflammatory cells			
-~+	4 (33.3)	18 (40.9)	0.634
++~+++	8 (66.7)	26 (59.1)	
Pathology stage‡			
I	0 (0.0)	6 (13.6)	0.454
II	11 (91.7)	35 (79.5)	
III	1 (8.3)	3 (6.8)	
Solar elastosis			
Yes	1 (8.3)	0 (0.0)	0.214
No	11 (91.7)	44 (100)	
Pigmentation of the primary			
Amelanotic	6 (50)	13 (29.5)	0.185
Pigmented	6 (50)	31 (70.5)	
Cellular morphology			
Epithelioid cells	6 (50)	35 (79.5)	0.040
Spindle cells	6 (50)	9 (20.5)	

†Abbreviation: LMM, lentigo maligna melanoma; ALM, Acral lentiginous melanoma; NM, Nodular melanoma; ‡None of ALM in the IV stage; *Categorical variables were compared using Chi-square test or Fisher's exact test.

was difficult to characterize and study this particular melanoma subtype in Caucasians because of its relatively low incidence rate. ALM patients tend to be older in age, have fewer atypical nevi and have a lower incidence of chronic sun-induced damage compared with other types of melanoma.

Our hospital has a melanoma center mainly composed of yellow skinned Chinese patients which enabled us to study its association with trauma. The racial background of ALM is interesting, as it occurs in lower proportion of Asian who are usually at high risk for melanoma.

The patients notice a lesion with greater Breslow thickness and ulceration only after trauma. Many factors seem to contribute to the delay of diagnosis: elderly patients, frequent lack of pigmentation, hidden sites and unusual presentation. Significant delays appear to result from the patients' negligence. Some take the inappropriate disposition which include cutting off the lesion tissue with scissors or using the Chinese herbal medicine externally. There were several patients whose hyperpigmentation were diagnosed as nevus and took laser treatments in the early stage of PTM.

The statistical incidence ratio of our data in female are remarkably lower than male, besides, in the group of PTM, ratio in female was even lower, which might explain the fact that biological, environmental and behavioral factors of different genders in melanoma have an influence on incidence and outcome [3].

All authors agreed that the median age at onset of ALM is higher than in overall cases of melanoma [4]. In our study, the median age was 70 years, with a peak incidence during the seventh decade with the higher median age. It was reported that the number of ALM occurring on the feet has previously been found to be about 5 to 16 times higher than on the hand [5-7], but in our cases, the comparison between feet and hands were 10 times higher (50:6), this data seem consistent with other published data of the 56 ALM.6 (10.7%) occurred on the hands and all of them in the finger nails, 50 (89.3%) on the feet, the majority of them were in the heels or plantar. It

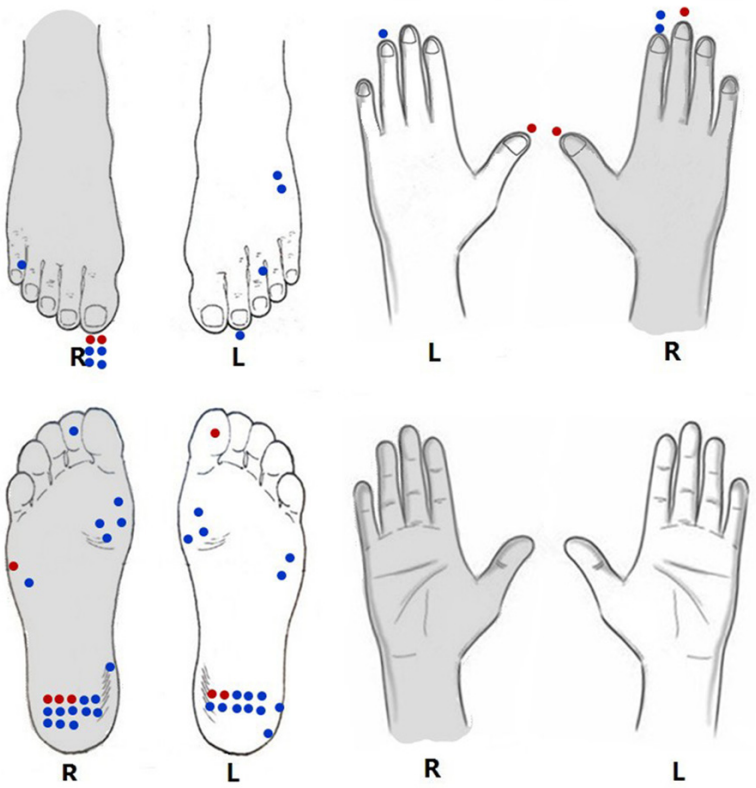

Figure 1. Precise location of the 56 acral lentiginous melanoma. The red spot is Post trauma melanoma, the blue spot is Trauma unrelated melanoma. For subungual location, the spot is in front of the involved digit, the right hand and foot painted gray.

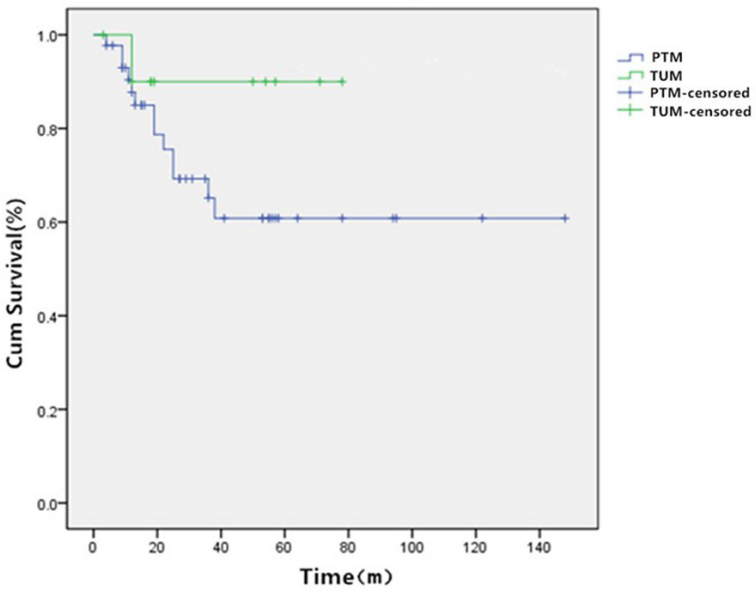

Figure 2. Kaplan-Meier survival curves of melanoma-specific survival †PTM: Post trauma melanoma; TUM: Trauma unrelated melanoma.

was confusing to find that melanoma on hands predominated on subungual areas and rarely involved the palm, whereas, melanoma with feet predominated on the soles and was proportionally quite rare on dorsum pedis areas. The frequency of traumatic events was reported to vary from 25% to 55% [8-12], this finding is higher than the result of our data (12 in ALM had traumatic events, 21.4%).

Some of the classical risk factors for melanoma, such as fair skin type, sun exposure and family or personal history of previous melanoma, seem to be less important in acral lesions and it is difficult to accept the role of direct sun exposure in subungual or volar skin which is usually protected by clothing and covered by a thick stratum corneum or nail plate. Some pathological associations have reported UV exposure associated with ALM, but without a proven link [13]. In our series, ALM has been rarely contracted with excessive UV exposure, only one patient had UV exposure on the right thumb finger nail.

Otherwise, the study by Durbec et al [7], previous trauma and nevus on the soles or toes were identified as two main risk factors in case-control studies. As the pathogenesis of ALM is currently unclear, differential responses of melanocytes to mitogenic stimulus according to site, and anatomical variations in the density of melanocytes could also play a role in the anatomical distribution of ALM [7]. Trauma has been suggested to be a possible major triggering factor where the PTM was liable to happen in the anatomical locations with weight bearing or the dominant feet or hands which could be easily injured (**Figure 1**).

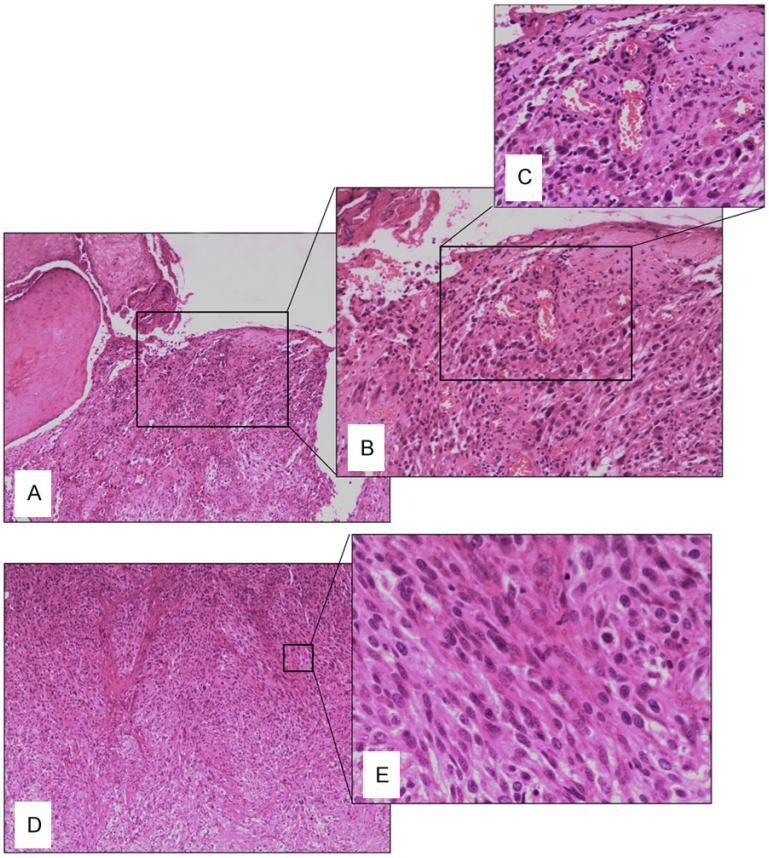

Figure 3. Plantar of the right foot in Post-trauma melanoma (A-C). Overview and original magnification (hematoxylin and eosin staining (H&E) A × 4; B × 10; C × 20), Melanoma with with microvascular proliferation and expansion. D, E. Overview and original magnification (hematoxylin and eosin staining (H&E) D × 4; E × 20), Post traumatic melanoma with spindle cells and amelanotic.

It is the same as TUM because the traumatic events have rarely been proven to be a cause of melanoma at any other site. Mohrle and Hafner [14] hypothesized a link between trauma history and melanoma because of the strong preponderance of the subungual melanoma on the thumbs or the great toes, which are more exposed to trauma. Moreover, this striking feature was found on the heels and plantar of the feet in our data. Another interesting feature was that the non-healing foot ulcer of PTM was similar to the diabetic foot ulcer, which was more prone to happen in the anatomical locations with weight bearing or the dominant feet or big toes [15]. Moreover, there has been reports that a non-healing foot ulcer interpreted as a diabetic ulcer, which after 2 years has been diagnosed as acral melanoma with satellitosis [16]. Diagnosis of ALM can be challenging because traditional diagnostic criteria for melanomas elsewhere in the body based on asymmetry, border irregularity, multiple colors, a diameter of 6 mm or larger, or evolution of any of these features (ABCDE) [17] can be difficult to ascertain. The common thing between melanoma and diabetes is vasculogenisis, which occurs in pathological conditions of malignant melanoma. It was first described by Kroghin 1919 [18], which showed vasculogenisis is physiologically tightly regulated during embryogenesis, wound healing and in pathological conditions of tumor growth and diabetes [19]. In our pathological observation, it was found that most of the PTM was associated with microvascular proliferation and expansion, more spindle cells and amelanotic compared to TUM (**Figure 3**).

In literatures, some authors described that besides local cellular damage due to sunlight, blisters, scarring processes [20], trauma as well as hormonal, feverish processes and myelodysplastic have also been observed prior to the development of eruptive nevi. Some researchers have also shown that blood-borne stimulation of preexisting disseminated nevus nests by cytokines might play an additional role. These changes in blood vessels might easily cause PTM and non-healing of the sites. Trauma is a possible major risk factor to cause inflammation and non-healing foot ulcer. In other word, trauma is merely a precipitating factor for ALM and it could explain the occurrence of more ulcerations in PTM than in the TUM as shown in our data (it had a statistically significantly with ulceration between PTM and TUM, $P < 0.05$). Presence of ulceration in PTM was significantly associated with vasculogenisis and unexpected inflammation while ulceration of TUM can also be associated with advanced tumor (i.e., stage II or above). Cases in which traumas immediately preceded the

discovery of melanoma should be considered in order to draw the patient's attention to the lesion. Paying attention to the lesion play an important role in protecting us from advanced stage. This may be one of the explanations for the fact that the prognosis of PTM are better than TUM with higher proportion of ulceration (Some authors identified ulceration of the primary tumors and the Clark level as important parameters [21]).

In addition, Maria Angelica Selim studied a series of 92 nonsurgical traumatized melanocytic nevi. Cases were analyzed for histologic evidences of architectural and cytology criteria associated with atypia [22]. There was a report [23] of a case of a 16-year-old girl with a suspected pigmented macule on her right knee that appeared after trauma. The lesion was completely excised and diagnosed as tumoral melanosis (TM), which may be considered as a possible trigger for this histiocytic response of abundant pigments. Trauma can also be associated with hyperpigmentation and wound-healing processes which produce chemokine that attract melanocytes, or it could suggest a non-canonical function of melanocytes in trauma repair [24].

Taking this information into account, the melanocytes can be easily affected by trauma and converted into atypical moles and increasing the risk of melanoma. Arlo J. Miller et al [25] reported that the effect of exposure to ultraviolet light is governed by variations in particular genes (polymorphisms), which affect both the defensive response of the skin to ultraviolet light and the risk of melanoma. In our data, the effect of exposure to ultraviolet light is not considerate, the trauma and inflammation may be governed by variations in particular genes. Shain, A. H. et al [26] sequenced 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions including unequivocally benign lesions, intermediate lesions, and intra epidermal or invasive melanomas. It defined the succession of genetic alterations during melanoma progression, showing distinct evolutionary trajectories for different melanoma subtypes. It also identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. The distribution of genetic alterations, copy-number changes point mutations and different area of individual cases revealed the phylogenetic history of each neoplasm. Therefore, we consider trauma and inflammation affect the phylogenetic history of ALM and the occurrence of neoplasm has a series of changes which include the one induced by trauma and inflammation.

In conclusion, ALM is the most commonly diagnosed pathological subtypes of malignant melanoma in Asians. In addition to genetic factors, trauma may also contribute to the development of melanoma. Strategies which aim the influence on progression and vasculogenisis of trauma and inflammation, a prerequisite for tumors, seem worthwhile to study. Further investigation to find a key finding of molecular genetic particularities which could lead to the use of specific target therapies is indispensable.

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Disclosure of conflict of interest

None.

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