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Clinicopathological Features of 106 Cases of Chinese Patients with Acral Melanoma

Hongyu Zhou[1]; Yangyang Ma[2]; Panpan Wang[1]*; Yige Zhao[1]; Chenyu Tang[1]; Ping Wang[2]

[1]Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Zhejiang Chinese Medical University, Hangzhou, 310009, China.

[2]Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Hangzhou Dermatology Hospital of Zhejiang University School of Medicine, Hangzhou, 310009, China.

Abstract

Objectives: This paper aims to characterize and study clinicopathological features of acral melanoma in Chinese patients.

Methods: The clinical and pathological data of patients diagnosed with AM in Hangzhou Third People's Hospital from October 2016 to October 2020 were collected, and their clinicopathological characteristics were retrospectively analyzed.

Results: A total of 106 patients were included in the study, including 58 females (54.72%) and 48 males (45.28%). The age of the patients ranged from 30 to 89 years old, with a mean age of 61.01 years old. The median disease duration was 3.00 years. There were 75 cases (70.75%) in the sole, 16 cases (15.09%) in the palm, 12 cases (11.32%) in the fingernail, and 3 cases (2.83%) in the toenail. In terms of risk factors, 6 cases (5.66%) were related to pigmented nevus, 7 cases (6.60%) had a history of trauma, and 6 cases (5.66%) had malignancy other than melanoma. In terms of histological types, there were 66 cases (80.49%) of superficial spreading melanoma (SSM), 12 cases (14.63%) of acral lentiginous melanoma (ALM), and 4 cases (4.88%) of nodular melanoma (NM). In terms of clinical stage, 22 cases (20.75%) were in situ, 20 cases (18.87%) were in stage I, 56 cases (52.83%) were in stage II, 6 cases (5.66%) were in stage III, and 2 cases (1.89%) were in stage IV. Sole melanoma included 12 cases in situ (16.00%), 12 cases in stage I (16.00%), 47 cases in stage II (62.67%), 3 cases in stage III (4.00%), and 1 case in stage IV (1.33%). Palm melanoma included 6 cases in situ (37.50%), 5 cases in stage I (31.25%) and 5 cases in stage II (31.25%). Subungual melanoma included 4 cases in situ (26.67%), 3 cases in stage I (20.00%), 4 cases in stage II (26.67%), 3 cases in stage III (20.00%) and 1 case in stage IV (6.67%). Based on the level of invasion, 22 cases (20.75%) were Clark level I, 13 cases (12.26%) were Clark level II, 24 cases (22.64%) were Clark level III, 44 cases (41.51%) were Clark level IV, 3 cases (2.83%) were Clark level V. The most common invasion level in sole melanoma was Clark level IV (37 cases, 49.33%), in palm melanoma was Clark level I (6 cases, 37.50%), in subungual melanoma was Clark level III (5 cases, 33.33%). The mean/median Breslow thickness of AM was 3.24 mm/2.85 mm. The mean/median Breslow thickness of sole, palm and subungual melanoma was 3.52/3.00 mm, 2.06/1.20 mm and 2.70/2.20

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Correspondance: *Ping Wang, Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Hangzhou Dermatology Hospital of Zhejiang University School of Medicine, Hangzhou, 310009, China. Email: dermwang@aliyun.com*

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mm, respectively. Tumor-infiltrating lymphocytes (TILs) of invasive AM were absent in 36 (42.86%), inactive in 35 (41.67%) and active in 13 (15.48%). TILs were absence in 49.21%, 10.00% and 36.36% of sole, palm and subungual melanoma, respectively.

Conclusion: Sole and subungual melanoma may be more aggressive than palm melanoma, with differences in clinical stage, Clark level, Breslow thickness, and TILs.

Keywords: Acral melanoma; Melanoma; Clinicopathologic feature; Epidemiology.

Abbreviations: SSM: Superficial spreading melanoma; LMM: Lentigo maligna melanoma; NM: Nodular melanoma; ALM: Acral lentiginous melanoma; AM: Acral melanoma; NAM: Non-acral melanoma; TILs: Tumor-infiltrating lymphocytes.

Introduction

Cutaneous melanoma is usually classified mainly into four main histological subtypes: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM) and acral lentiginous melanoma (ALM). Some authors use acral melanoma (AM) and ALM as interchangeable terms [1]. However, it is important to note that not all melanomas that arise on acral locations are ALMs, as they can also be of the nodular or superficial spreading subtypes [2]. For this manuscript we consider AM as all melanomas arising from sites such as the palms, soles, and nail beds.

Despite AM having the highest frequency among cutaneous melanoma in Chinese, few epidemiological data are available regarding it. Significant clinicopathological and survival heterogeneities exist between AM and melanoma occurring on the sun-exposed skin (non-acral melanoma, NAM). Melanomas driven by non-ultraviolet radiation are uncommon in sun-exposed sites but dominate those occurring in acral sites. Significantly mutated genes included BRAF, CDKN2A, NRAS, and TP53 in NAM, while BRAF, NRAS, and NF1 in AM [3]. And AM more frequently has KIT mutations when compared to NAM [4]. Therefore, AM should be acknowledged as a special subtype. Several previous studies suggested AM has a worse prognosis compared with NAM [5-9]. The first reason for the poor prognosis of AM is the delayed diagnosis. Previous epidemiological data show that patients with AM present a relatively advanced clinical stage at diagnosis. The study by Lv J et al showed that 33.8% of patients had lymph node metastasis at the time of diagnosis (clinical stage in III/IV) [9]. Delays in diagnosis is independent prognostic factors [8-10]. A study by Lino-Silva LS, which included 715 cases, showed that the 5-year disease-specific survival rates of AM patients with stages I, II, and III were 53.3%, 52.7%, and 40.8%, respectively [10]. There is a large difference in disease-specific survival rates between patients in the early and late stages.

Second, the poor prognosis of AM is also associated with its inherent adverse pathological features. Besides clinicopathological features including age, gender, ulcer, Breslow thickness, location, and tumor lymphocyte infiltration, [5,6,8-15], the expression of immunohistochemical markers such as ki-67, P16 can also influent the prognosis of AM [16,17].

Several recent studies have shown that the different primary site has a significant impact on clinicopathological features of AM, leading to different prognostic outcomes, but the conclusions are still controversial. A recent study by Wei X et al [14] showed that, compared with subungual and palm melanomas, sole melanomas have more adverse pathological features, such as thicker Breslow thickness, advancer stage, higher recurrence rate, and more distal metastases, which lead to poor prognosis. While the study of Holman BN [18] et al showed that subungual melanomas have a deeper thickness at diagnosis than sole and palm melanomas.

Despite its important clinical implications, few relevant studies have focused on the clinicopathological features of AM in China. In this article, the clinicopathological data of Chinese patients with acral melanoma were collected, described, and analyzed, including the history of pigmented nevi, gender, age, ulcer, stage, Breslow thickness, location, tumor lymphocyte infiltration, and expression of immunohistochemical markers which could supplement Chinese epidemiological data of AM, guide and inspire the next diagnosis and treatment of AM, and help predict the prognosis of patients.

Material and methods

Patients and samples

The cases with AM confirmed clinically and pathologically in Hangzhou Third People's Hospital from 2016 to 2020 were included. After several cases were excluded due to incomplete and missing clinicopathological data, 106 patients remained and were selected for the study.

Methods

Medical records were collected. The hematoxylin and eosin (H&E) stained sections and immunohistochemical slides were reviewed. The parameters include the gender, age at diagnosis, course of disease, location of lesion, ulceration, conscious symptoms, history of pigmented nevi or history of trauma, clinical stage, histological subtype, Clark level, Breslow thickness, tumor-infiltrating lymphocytes (TILs), and expression of immunohistochemical markers. The disease was staged in accordance with the American Joint Committee on Cancer (AJCC) staging system. Clark level, Breslow thickness, and TILs were depended on NCCN Guidelines (2022) and Chinese guidelines on standardized pathological diagnosis of melanoma (2021 version). All data were statistically analyzed with the software SPSS, version 19.0. Ordinal data and continuous variables with abnormal distribution were analyzed by rank-sum test. Categorical variables were analyzed by chi-square test. A P value less than 0.05 were considered statistically significant.

Results

From 2016 to 2020, a total of 117 cases of AM were diagnosed in our hospital, accounting for 59.4% of all cutaneous melanoma in our hospital in the past five years. After excluding ineligible

cases, a total of 106 cases of AM were included in the study, of which 75 were sole melanoma, 16 were palm melanoma, and 15 were nail bed melanoma. The clinicopathological data of the patients were summarized in Table 1.

Table 1: Clinicopathological features of acral melanoma.

Indicators total N=106	Totol n(%)	Soles n(%)	Palms n(%)	Nail beds n(%)	Statistics values	P-value
Age (Mean ± SD) Sex	61.01 ± 13.54	62.56 ± 13.49	56.75 ± 16.10	57.80 ± 9.59	1.728[a]	0.183
Male	48(45.28)	31(41.33)	9(56.25)	8(53.33)	1.641[b]	0.44
Female	58(54.72)	44(58.67)	7(43.75)	7(46.67)		
Ulceration status						
present	45(42.45)					
absent stage	61(57.55)					
0	22(20.75)					
I	20(18.87)					
II	56(52.83)					
III	6(5.66)					
IV Clark level	2(1.89)					
1	22(20.75)					
2	13(12.26)					
3	24(22.64)					
4	44(41.51)					
5 Breslow thickness	3(2.83)					
in situ	22(20.75)					
<1 mm	10(9.43)					
1-2 mm	16(15.09)					
2-4 mm	34(32.08)					
>4 mm	24(22.64)					
(invasive AM)n=84 TILs						
0	36(42.86)					
1	35(41.67)					
2 histological subtypes	13(15.48)					
SSM	66(80.49)					
ALM	12(14.63)					
NM	4(4.88)					
NA	2					

SSM: Superficial Spreading Melanoma; ALM: Acrallentiginous Melanoma; NM: Nodula Melanoma; NA: Data Not Available.
[a]One-way ANOVA. [b]Chi- square test. cKruskai H Test.

Overview of malignant acral melanoma in China

Epidemiologic feature

Of all patients 58 (54.72%) were women and 48 (45.28%) were men (female: male ratio, 1.21:1). The patients were between 30 and 89 years of age (mean age: 61.01 years).

Their disease course ranged from 2 days to 50 years, and the median disease duration in 106 patients was 3.00 years. In terms of past medical history, six patients (5.66%) had a history of malignancy other than melanoma, including 3 cases of lung cancer, 2 cases of prostate cancer, and 1 case of nasopharyngeal cancer. 7 patients (6.60%) had a history of trauma, and 6 cases (5.66%) were associated with nevus in histology. There were 75 cases (70.75%) in the sole, 16 cases (15.09%) in the palm, 12 cases (11.32%) in the fingernail, and 3 cases (2.83%) in the toenail. The ulceration rate of AM was 42.45%. 13 patients (12.26%) experienced pain, and 1 patient experienced significant pruritus.

Stage and histological features

In terms of clinical stage, 22 cases (20.75%) were in situ, 20 cases (18.87%) were in stage I, 56 cases (52.83%) were in stage II, 6 cases (5.66%) were in stage III, and 2 cases (1.89%) were in stage IV. Based on the level of invasion, 22 cases (20.75%) were Clark level I, 13 cases (12.26%) were Clark level II, 24 cases (22.64%) were Clark level III, 44 cases (41.51%) were Clark level IV, 3 cases (2.83%) were Clark level V. In terms of histological types of invasive AM, there were 66 cases (80.49%) of superficial

spreading melanoma (SSM), 12 cases (14.63%) of acral lentiginous melanoma (ALM), and 4 cases (4.88%) of nodular melanoma (NM). In 2 patients, histological subtype could not be determined due to extensive exfoliation. The mean/median Breslow thickness was 3.24/2.85 mm.

Acral melanoma has a variety of histological changes. According to a three-point scale for infiltrating lymphocyte grading recommended by AJCC, Tumor-infiltrating lymphocytes (TILs) of invasive AM were absent in 36 (42.86%), inactive in 35 (41.67%) and active in 13 (15.48%) . Lichenoid lymphocyte infiltrate was observed in 1 case (1.19%), and lymphocytes migrated into the epidermis in 2 cases (2.38%). Elongated, fused, or destructed rete ridges of epidermis were observed in 51 cases (60.71%), hyperplasia of fibrous tissue in 43 cases (51.19%), obvious vascular hyperplasia in 9 cases (10.71%), and necrosis in 12 patients (14.29%). Multinucleated giant cells were infiltrated in 8 cases (9.52%), plasma cells in 9 cases (10.71%), eosinophils in 3 cases (3.57%), and neutrophils in 2 cases (2.38%). Immunohistochemical staining revealed vascular or lymphatic infiltration in 7 cases (8.33%), perspiration epithelial cell infiltration in 8 cases (9.52%), and nerve infiltration in only 1 case (1.19%).

Differences in clinicopathological features of acral melanoma across the sole, palm, and nail bed

There were no significant differences in age (P=0.183), sex (P=0.440), ulcer (P=0.192), and histological subtypes (P=0.383) among the three groups.

Stage

Sole melanoma included 12 cases in situ (16.00%), 12 cases in stage I (16.00%), 47 cases in stage II (62.67%), 3 cases in stage III (4.00%), and 1 case in stage IV (1.33%). Palm melanoma included 6 cases in situ (37.50%), 5 cases in stage I (31.25%) and 5 cases in stage II (31.25%). Subungual melanoma included 4 cases in situ (26.67%), 3 cases in stage I (20.00%), 4 cases in stage II (26.67%), 3 cases in stage III (20.00%) and 1 case in stage IV (6.67%). There were statistically significant differences in the clinical stage among the sole, palm, and nail bed groups (P=0.032).

Clark level

The most common invasion level in sole melanoma was Clark level IV (37 cases, 49.33%), in palm melanoma was Clark level I (6 cases, 37.50%), in subungual melanoma was Clark level III (5 cases, 33.33%). Clark level IV-V was observed in 52.00% of sole melanoma, which was much higher than that of subnail melanoma (26.67%) and palm melanoma (25.00%). There were statistically significant differences in Clark level among the sole, palm, and nail bed groups (P=0.023).

Breslow thickness

The mean/median Breslow thickness of sole melanoma, subungual melanoma, and palm melanoma was 3.52/3.00 mm, 2.70/2.20 mm, and 2.06/1.20 mm, respectively. The proportion of thickness greater than 2 mm was higher in sole melanoma (62.67%) than in the nail bed group (46.67%) and palm group (26.67%). The results were statistically significant. (P=0.019).

Tumor-infiltrating lymphocyte

Sole melanoma tends to have fewer TIL than subungual and palm melanoma (P=0.021). In the sole, subungual, and palm groups, the proportions of TIL defined as brisk were 11.11%, 18.18%, and 40.00%, and the proportions defined as non-brisk were 39.68%, 45.45%, and 50.00%, respectively.

An expression of immunohistochemical markers in acral melanoma

HMB-45 staining was positive in 88 of 91 (96.70%), Melan-A in 90 of 92 (97.83%), S100 in 83 of 89 (93.26%), Sox10 in 76 of 81 (93.83%). In addition, 42 of 45 (93.33%) stained for MITF, 53 of 58 (91.38%) for tyrosinase,39 of 41 (95.12%) for vimtin, and 25 of 33 (75.76%) for Bcl-2. P16 staining was positive in 26 of 58 (44.83%), P53 in 3 of 7 cases (42.86%), P63 in 4 of 8 (50%). CD63 was positive in 9 of 11 cases (81.82%),and Cyclin D1 in 3 of 4 cases (75%). 52.13% of patients had a Ki-67 proliferation index less than 20%.

Discussion

From 2016 to 2020, the number of AM patients diagnosed in our hospital has increased rapidly year by year, in line with the trend of increasing incidence of melanoma in recent years. Most AM patients of China in previous studies were in clinical stage II/III [9,14], but the patients diagnosed in our hospital were mainly in situ and local invasive stage (stage I/II), which was related to early diagnosis. The reasons for early diagnosis are as follows: Firstly, the vast majority of melanoma patients in our hospital are managed by dermatologists, and the preliminary clinical diagnosis of dermatologists helps to detect AM at an early stage. Secondly, Socioeconomic factors resulting in patients with pigmented lesions in the acral area will seek medical treatment as soon as possible. The medical history has a certain influence on the clinicopathological characteristics, and the study of Scalvenzi M et al [19] showed that there are histopathological differences between de novo melanoma and naevus-associated melanoma. The possibility of malignant melanoma arising from benign melanocytic nevus remains controversial. Several studies suggest that nearly 1/3 of melanomas are secondary to melanocytic nevus [20-22], while the study by Scalvenzi M et al [19] found that only 8.4% of melanomas were. This proportion appears to be higher when the definition is based on information provided by the patient than when it is based on histology due to different determination criteria [23]. In addition, the proportion may vary according to race, region, and hospital selection bias. Our determination criteria were histological evaluation or history of pathologically confirmed nevi. The result shows that nevus-associated melanoma accounted for 5.66% of AM. We believe that in the acral area, the majority of melanomas are de novo and a small proportion is nevus-associated.

Trauma is a factor associated with increased risk for melanoma formation [24]. The study of Zhang N et al [25] suggested showed a higher risk of developing post-trauma melanoma in the feet and hands than in other sites. Our results suggest that 6.60% of AM is trauma-related.

Some authors use AM and ALM as interchangeable terms [1]. Our study shows that the most common histological type of AM in Chinese is SSM, followed by ALM and NM, so the terms AM and ALM should not be used interchangeably.

Sole is the most common primary site in AM in Chinese, and subungual melanoma is more common in fingernails than toenails. Several recent studies [14,18,26] have shown that AM from three primary sites has different prognoses, but the conclusions are controversial. The study by Holman BN [18] et al showed that patients with subungual melanoma had a worse prognosis compared with those with melanoma arising on palms and soles, but recently a study from a large sample size by Wei X et al [14] showed patients with sole melanoma had a worse prognosis compared with the other two groups. The reason for the difference in survival rate between the three groups may be the difference in clinicopathological features such as clinical stage, Breslow thickness and ulcer. The study of Wei X et al [14] showed a deeper Breslow thickness in the sole melanoma group, which is consistent with our findings. However, they believed that sole melanoma had the highest clinical stage, which was different from our study.

Our study showed that sole and nail bed melanoma had a more advanced clinical stage, deeper Clark level, and Breslow thickness compared to palm melanoma. Sole melanoma has a higher Clark level and deeper Breslow thickness compared to subnail melanoma. In terms of clinical stage, compared with the sole group and nail bed group, the palm group had the lowest clinical stage, with in situ melanoma in 37.50% of cases and local invasive melanoma in the rest. Subungual melanoma has a higher probability of melanomas in clinical stages III/IV (26.67%) compared with sole melanoma (5.33%). However, in situ melanoma was more commonly observed in subungual melanoma (26.67%) rather than sole melanoma (16.00%) whereas invasive melanoma represented 73.33% of subungual melanoma and 84.00% of sole melanoma. The results of this study showed that the proportions of stage Ⅰ and stage Ⅱ were 16.00% and 62.67% for sole melanoma, 31.25% and 31.25% for palm melanoma, 20.00% and 26.67% for subungual melanoma, respectively. This may be related to the average Breslow thickness ranking from thick to thin as sole, palm, and subungual melanomas. Metastatic melanoma (stage III/IV) accounts for 5.33% of sole melanomas and 26.67% of subungual melanomas, because metastasis depends on tumor N and M stages rather than tumor T stages, which are determined by Breslow thickness. In addition, it may also be related to the relatively small sample size of our metastatic melanoma patients.

Studies have shown that a higher amount of TILs in AM is associated with longer survival [16,27], which suggests that few TILs also associated with poor prognosis in AM. The study by Lee WJ et al [28] showed a higher amount of TILs in non-subnail acral melanomas than in subnail melanomas, but considering the heterogeneity of clinicopathological features of AM arising from the three different primary sites, the samples were carefully divided into three groups of sole, subungual, and palm melanomas for the evaluation of TILs. It was found that sole melanoma had the fewest TILs, followed by subungual melanoma and palm melanoma. These results suggest that there is indeed inherent heterogeneity in the clinicopathological features of AM at different primary sites.

Even though histologic examination remains the gold standard in the diagnosis of melanoma, immunohistochemistry staining techniques are very important to the diagnosis of melanoma to reduce the incidence of misdiagnosis. Immunohistochemistry can not only help to diagnose melanoma but also reflect the functional characteristics of the tumor. Melan-A and HMB45, melanocyte-specific markers, showed high positive rates of 97.83% and 96.70% respectively in our study, which is most sensitive. Ki-67 is a well-used cell proliferation marker, and a Ki-67 proliferation index of ≥20% was associated with shorter overall survival of melanoma [17]. The Ki-67 proliferation index was less than 20% in 52.13% of patients in our study, which may be related to the fact that most of our patients were with early-stage melanoma.

There are several limitations of our study. First, since we selected the latest samples for research, it is currently impossible to carry out a long-term prognosis evaluation. In the future, we will continue to follow up to analyze the relationship between clinicopathological features and survival rate. Second, we assessed the total number of TILs without differentiating their immunophenotypes. Immunophenotypes of TILs also play an important role in the prognosis of melanoma. A Single-cell RNA-sequencing study [29] revealed the heterogeneity of CD8+ T cell subpopulations in melanoma, finding that high infiltration of exhausted CD8+ T cell subpopulation 2 could contribute to poor prognoses. Further studies are needed to determine whether there are differences in lymphocyte immunophenotypes in AM arising from different primary sites. Tired, the expression of immunohistochemical markers was qualitative but not quantitative, which may result in the omission of some statistically significant results. The relationship between immunohistochemical markers and clinicopathological features still needs further study.

Conclusion

Sole and subungual melanoma may be more aggressive than palm melanoma, with differences in clinical stage, Clark level, Breslow thickness, and TILs.

Declarations

Disclosure: The authors report no conflicts of interest related to this work.

Declaration consent: This is an observational study. The Hangzhou Third People's Hospital Research Ethics Committee has confirmed that no ethical approval is required.

Authorship contribution statement:

1. Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Yangyang Ma: Visualization, Funding acquisition: Hongyu Zhou
2. Acquisition of data, review and editing: Masaki Fujioka
3. Acquisition of data, review and editing: Yige Zhao
4. Acquisition of data, review and editing: Chenyu Tang
5. Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization: Ping Wang

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