Original Article

Melanoma: Differences between Asian and Caucasian Patients

Haur Yueh Lee,[1] *MBBS, MRCP (UK), FAMS*, Wen Yee Chay,[2] *MBBS, MRCP (UK)*, Mark BY Tang,[3] *MBBS, MRCP (UK), FAMS*, Martin TW Chio,[3] *MB Ch B (Bristol), MRCP (UK), FAMS*, Suat Hoon Tan,[3] *MMed (Int Med), DipRCPath (DMT), FAMS*

Abstract

Introduction: Cutaneous melanoma is rare in Asia and the clinical presentation and outcome of melanoma is not well described in Southeast Asia. In addition, it is unclear if ethnic variations exist between the various racial groups. The objective of our study is to present the clinical characteristics of melanoma in Singapore and to highlight ethnical differences between Asians and Caucasians living in Singapore. Materials and Methods: Data were retrospectively collected from 48 patients with histological confirmation of melanoma who were seen in both the National Skin Centre and National Cancer Centre of Singapore. Results: Acral lentiginous melanoma (ALM) was the most common subtype of melanoma in Singapore (50%). A higher proportion of non-ALM subtypes of melanoma compared to ALM were diagnosed at stage 1 (48% vs. 25%). The delay in diagnosis of ALM was 27 months compared to 12 months in other subtypes. Compared to Caucasians, there was a trend towards Asian patients being older, having a higher proportion of ALM and a longer delay to diagnosis. Conclusion: Geographical and ethnic variations in the clinical presentation of melanoma exist. Specially adapted programmes are necessary to increase awareness of the different clinical presentation of melanoma in Asia and to encourage examination of the palms and soles in order to reduce the delay in diagnosis.

Ann Acad Med Singapore 2012;41:17-20

Key words: Acral, Pigmented lesions, Singapore, Skin cancer

Introduction

Cutaneous melanoma is the most common cause of mortality amongst skin cancer in Caucasian populations[1,2] and incidence rates per 100,000 patient years vary between 21.9 in the United States to 55.9 in Australian males.[3] In contrast, the incidence of melanoma in Asia is significantly lower with incidence rates of 0.2 to 0.5 per 100,000 patient years.[4,5] In addition, the most common histological subtype in Asians is acral lentiginous melanoma (ALM) which accounts for approximately 50% of all cases,[6,7] compared to Caucasians populations where it constitutes only 2% to 3% of all cases.[8]

Singapore is a multi-ethnic country, located in equatorial Southeast Asia with a resident population of 3.8 million consisting of Chinese (77%), Malays (14%), Indians(8%) and 1% of other races, as well as a non-resident population of 1.2 million of various ethnicities.[9] There have been few reports on the features of melanoma in Asia, particularly in Southeast Asia. Our current study aims to clarify the clinical presentation of cutaneous melanoma in Singapore and to evaluate if ethnic variations exist.

Materials and Methods

All cases of cutaneous melanoma seen at both the National Skin Centre and the National Cancer Centre (which are tertiary referral centres for skin diseases and cancers respectively) between 1998 and 2008 were retrospectively analysed. Patients with a coded diagnosis of melanoma were obtained from the institution's computer database. Only cases with histological diagnosis of melanoma were included in this study. The medical records and histological reports were systematically reviewed and information pertaining to demographics, clinical presentation, histological features, other clinical investigations, treatment modalities and follow-up data were recorded. Staging of the melanoma was carried out according to the American Joint Committee on Cancer staging system (2002).

The time-interval to diagnosis was defined as the duration between the onset of the new pigmented lesion, change in an existing mole or previous normal surveillance and the diagnosis of melanoma.

To evaluate if histological subtypes and ethnicity

[1]Dermatology Unit, Singapore General Hospital
[2]Department of Medical Oncology, National Cancer Centre
[3]National Skin Centre
Address for Correspondence: A/Prof Tan Suat Hoon, National Skin Centre, Singapore, 1 Mandalay Road, Singapore 308205.
Email: shtan@nsc.gov.sg

influenced the presentation and outcome of disease, subgroup analysis of ALM versus non-ALM cases as well as Asian cases (consisting of both residents and non-residents) versus Caucasian cases were performed.

Statistical analyses were performed using Statplus for Macintosh. In the analysis of cases, Fisher's exact test was utilised for qualitative variables and the Student's T test for quantitative variables. *P* values were double sided with *P* <0.05 taken for statistical significance. The small sample size precluded further multi-variable analyses.

Results

From the initial database of patients coded for melanoma, 17 cases were excluded (benign histology n = 13, unavailable histological reports/specimens n = 4) and a total of 48 cases were eventually included in the study. The clinical and pathological features are summarised in Table 1. The mean age of the patients was 60 years with range between 29 and 95 years). There were 27 males and 21 females with a male to female ratio of 1.3 : 1. Thirty-eight cases were diagnosed in the resident ethnic population (37 Chinese and 1 Indian) and the remaining 10 cases were diagnosed in the non-residential expatriate population (consisting of 3 Asians and 7 Caucasians). Distribution of the lesions include the palms and soles (n = 21), limbs (n = 10), trunk (n = 9), head and neck (n = 4) and nails (n = 4).

ALM was the most common histological subtype (Fig. 1), accounting for 50% of all cases (n = 24), followed by superficial spreading melanoma 37.5% (n = 18) and nodular melanoma 12.5% (n = 6). The mean Breslow's tumour thickness was 2.3 ± 2.0 mm. When stratified according to histological subtypes, the mean thickness of ALM subtypes was 2.5 ± 2.3 mm in comparison with non-ALM subtypes which was 1.7 ± 2.0 mm (*P* = 0.30). Thirty-six percent of patients presented with early stage melanoma (Stage I), when stratified according to histological subtypes, 48% of non-ALM were diagnosed at stage I compared to 25% of ALM (*P* = 0.07) (Table 2).

Surgical excision was the primary treatment modality in all patients. Ten patients (21%) who initially presented with stage I-III disease recurred after primary excision (Stage I: n = 3, Stage II: n = 5, Stage III: n = 2). Mean duration to tumour recurrence following initial diagnosis of melanoma was 25 months (range, 4 to 60 months).

The mean duration to diagnosis of melanoma for the total group of melanoma was 20 months (range, 1 to 120 months). The mean duration prior to diagnosis of ALM was 27 ± 33 months compared to 12 ± 14 months in other subtypes (*P* = 0.05). When stratified against ethnicity, the delay was 22 ± 28 months versus 7 ± 5 months for Asians versus Caucasians (*P* = 0.09) (Table 3).

Table 1. Clinical and Pathological Characteristics of Patients with Cutaneous Melanoma

Age (n = 48)	**No. of patients (%)**
<41	9 (19%)
41-50	4 (8%)
51-60	11 (23%)
61-70	12 (25%)
>71	12 (25%)
Gender (n = 48)	
Male	28 (58%)
Female	20 (42%)
Race (n = 48)	
Residents (N = 38)	
• Chinese	37 (77%)
• Malays	0 (0%)
• Indians	1 (2%)
Non-residents (N =10)	
• Asians *	3
• Caucasians #	7
Site of Primary Lesions (n = 48)	
Palms and Soles	21 (44%)
Limbs	10 (21%)
Trunk	9 (19%)
Head and Neck	4 (8%)
Nails	4 (8%)
Histological subtypes (n = 48)	
Acral lentiginous melanoma	24 (50%)
Superficial Spreading Melanoma	18 (37.5%)
Nodular melanoma	6 (17.5%)
Breslow's Thickness (n = 44) +	
Mean (mm)	2.3 ± 2.0mm
<1.0 mm	17
1.01-2.0 mm	9
2.01-4.0 mm	12
> 4.0 mm	6
Clark's level (n = 44)+	
Level I	2 (5%)
Level II	5 (11%)
Level III	16 (36%)
Level IV	15 (34%)
Level V	6 (14%)
Ulceration (n = 48)	17 (35%)
Staging (n = 44)+	
I	16 (36%)
II	23 (52%)
III	4 (9%)
IV	1 (2%)

* Burmese, Indonesian, Thai :1 each, # American N=2, English N=2, Swiss, Norwegian, French : 1 each. + Full staging information for 4 patients were missing.

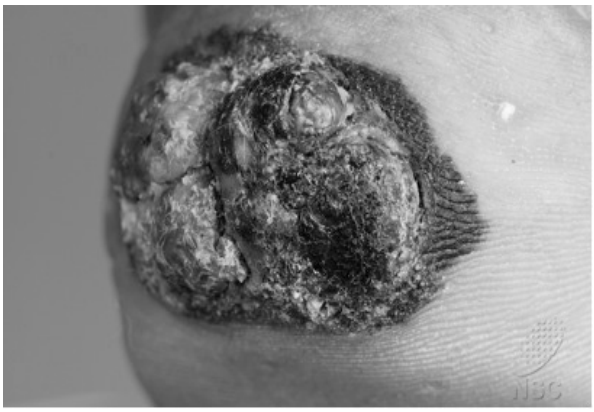

Fig. 1. Verrucous melanoma over the right heel.

Table 2. Comparison of Clinico-pathological Characteristics between Acral Lentiginous (ALM) and other Subtypes of Melanoma

Parameters (Frequencies and percentages if not stated otherwise)	ALM (n = 24)	Non ALM (n = 24)	*P* value
Gender			
Male	13 (54)	14 (58)	1.00
Female	11 (46)	10 (42)	
Ethnicity			
Asian	23	18	0.09
Caucasian	1	6	
Age (years)	63 ±19	57 ± 15	0.13
Mean Breslow	2.5 ± 2.3	1.7 ± 2.0	0.31
Staging (%)*			
I	5 (25)	11 (48)	0.29
II	14 (65)	9 (39)	
III	2 (10)	2 (9)	
IV	0 (0)	1 (4)	
Time to diagnosis (months)	27.0	12.0	0.05
Relapse	6 (25)	4(17)	0.47

* Full staging details are missing in 3 patients with ALM and 1 patient with Non-ALM

Discussion

Cutaneous melanoma is a rare malignancy in Singapore. Based on national cancer registry reports, incidence rates range from 0.3 per 100,000 to 0.5 per 100,000 patient-years.[5] Interestingly, despite the multi-ethnicity of the resident population, there was an over-representation of Chinese patients, with 37 Chinese patients out of the 38 resident cases. The only other reported case was in an Indian patient and no cases were seen among Malays. Sng *et al*[5] previously reported an estimated age adjusted incidence rate between the ethnic Chinese compared to the Malays and Indian populations as 1.2 times and 1.9 times higher respectively.

Table 3. Comparison of Clinico-pathological Characteristics between Asians and Caucasians

Parameters (Frequencies and percentages if not stated otherwise)	Asians (n = 41)	Caucasians (n = 7)	*P* value
Gender			
Male	23 (56)	4 (57)	1.00
Female	18 (44)	3 (43)	
Age (years)	62 ± 18	52 ± 11	0.09
Histological subtypes			
ALM	23 (56)	1 (14)	0.09
SSM	14 (34)	4 (57)	
NM	4 (10)	2 (29)	
Staging*			
I	13 (34)	3 (50)	0.77
II	20 (53)	3 (50)	
III	4 (11)	0	
IV	1 (2)	0	
Time to diagnosis (months)	22.8 months	7.4 months	0.09
Tumour recurrence	10 (24)	0	0.14

*Full staging details are missing in 3 Asian patients and 1 caucasian patient

ALM: Acral lentiginous melanoma; SSM: Superficial spreading melanoma; NM: Nodular melanoma

These results suggest that even within Southeast Asia, inter-ethnic variations exists and such differences may be due to intrinsic skin phototype, genetic factors, sun-seeking behaviour, clothing style or disease awareness.

In our current study, ALM was the most common histological subtype representing 50% of all cases. This result is similar to other Asian Chinese cohorts, where ALM accounts for 58%[10] and 51% of melanoma[6] in Taiwan and Hong Kong respectively. This is in contrast to western populations where ALM represents 2% to 3% of all melanoma.[8] Biological differences exist between the different subtypes of melanomas. UV exposure is not considered a risk factor for ALM and genetic variations of BRAF and N-Ras in the MAPK pathway as well as in expression of CDK4 and CCND1 genes have been described among the various subtypes of melanoma.[11] In addition, the prognosis of ALM is often poorer. Patients with ALM present with thicker lesions, more advanced stages and the 10 year survival is 10% to 20% lower than other subtypes of melanoma, even after adjusting for lesional thickness.[8] Similar trends were seen in our study—the mean depth of ALM was 2.5 mm compared to 1.7 mm in non-ALM and the proportion of patients with ALM appearing in stage I was also lower (25%) compared to other subtypes (48%).

A possible explanation for the more advanced presentation of ALM in our study is the delay in the diagnosis. The mean duration between the diagnosis and the appearance of signs and/or symptoms of cutaneous melanoma was 20 months. The delay was even greater in the ALM subtype with an average of 27 months compared to 12 months in other histological subtypes. In addition, when the Asians were compared to non-resident Caucasian cases, the delay in diagnosis was 22 months and 7.4 months respectively. An earlier local study has also shown that the delay in diagnosis was on average 1.6 years.[12] Although patient factors such as lack of knowledge and skin awareness are important contributors to delay,[13,14] of equal importance is the failure to suspect or diagnose ALM clinically among healthcare providers. Although no Asian studies have been performed, in Caucasian populations, one third of all ALMs were initially diagnosed as benign lesions. These misdiagnoses included viral warts, calluses, tinea pedis, foreign body reactions, non-healing foot ulcers, nevi, keratoacanthoma, as well as nail disorders such as onychomycosis, subungal hematoma and ingrown toenails.[15] In another study, 20% of palmoplantar melanoma were initially misdiagnosed and this proportion was even higher (52%) in subungual lesions. This misdiagnosis resulted in a median delay of 12 months in palmoplantar lesions and up to 18 months in subungual lesions.[16] Franke *et al*[17] reported that patient and physician factors resulted in a delay in diagnosis of ALM by 4.8 years and 7 months respectively.

All patients received surgical excision as the primary form of therapy and amongst the patients who presented in stage I to III, 21% had recurrence of the melanoma within a mean of 25 months (range, 4 to 60 months) after initial diagnosis. The recurrence rate of ALM in our study was 25% and this is similar to the French experience where 30% of ALM had a recurrence after a median of 1.6 years with 50% of them occurring during the initial 18 months and 75% occurring during the first 3 years.[18] In the recent years, sentinel node sampling and PET screening have been adopted in the management of patients and long-term follow-up will be required to evaluate the clinical outcomes.

Our study had several limitations. This was a retrospective study with the inherent flaws of incomplete data collection especially with regards to other epidemiological risk factors such degree of lifetime sun exposure, family history. The numbers of cases in our study were small but this is a reflection of the prevailing incidence of melanoma within our geographical context. The small sample size precluded significant univariate and multivariate analyses but certain variables showed a trend to effect.

Nonetheless, we have shown that in Singapore, there is a significant delay in the diagnosis of melanoma particularly in Asians presenting with ALM. This highlights the need for adapted education programmes emphasising the unique presentation of melanoma in Asia as well as to encourage the examination of the palms and soles as a part of self and physician directed skin examination.

Acknowledgements

We would like to acknowledge Dr Audrey Tan, Dr Donald Poon, doctors of the Skin Cancer Clinic, National Skin Centre and National Cancer Centre (NCC) for their initial work.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
2. Geller AC, Swetter SM, Brooks K, Demierre M, Yaroch AL. Screening, early detection and trends for melanoma: Current status (2000-2006) and future directions. J Am Acad Dermatol 2007;57:555-72.
3. Garbe C, Mcleod GRC, Buettner PG. Time trends of cutaneous melanoma in Queensland, Australia and Central Europe. Cancer 2000;89:1269-78.
4. Tanaka H ,Tsukuma H, Tomita S, Ajiki W, Kitagawa T, Kinoshita N, et al. Time trends of incidence for cutaneous melanoma among the Japanese population: an analysis of Osaka cancer registry data: 1964-95. J Epidemiol 1999:9 (Suppl. 6): S129-35.
5. Sng J, Koh D, Wong CS, Tai BC. Skin cancer trends among Asians living in Singapore from 1968-2006. J Am Acad Dermatol 2009;61:426-32.
6. Luk NM, Ho CL, Choi CL, Wong KH, Yu KH, Yeung WK. Clinicopathological features and prognostic factors of cutaneous melanoma among Hong Kong Chinese. Clin Exp Dermatol 2004;29:600-4.
7. Chen YJ, Wu CY, Chen JT, Shen JL, Chen CC, Wang HC. Clinicopathologic analysis of malignant melanoma in Taiwan. J Am Acad Dermatol 1999;41:945-9.
8. Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma. Incidence and survival patterns in the United States 1986-2005. Arch Dermatol 2009;145:427-34.
9. Singapore Department of Statistics. Statistics Singapore: population (mid-year estimates). Available from: URL: http:// www.singstat.gov.sg/stats/themes/people/hist/popn.html. Accessed January 4, 2011
10. Chang JWC, Yeh KY, Wang CH, Yang TS, Chiang HF, Wei FC, et al. Malignant melanoma in Taiwan: a prognostic study of 181 cases. Melanoma Res 2004;14:537-41.
11. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H et al. Distinct sets of genetic alterations in melanoma. N Eng J Med 2005;353:2135-47.
12. Tan E, Chua SH, Lim JT, Goh CL. Malignant melanoma seen in a tertiary dermatological centre, Singapore. Ann Acad Med Singapore 2001;30:414-8.
13. Betti R, Vergani R, Tolomio E, Santambrogio R, Crosti C. Factors of delay in the diagnosis of melanoma. Eur J Dermatol 2003;13:183-8.
14. Krige JE, Isaacs S, Hudson DA, King HS, Strover RM, Johnson CA. Delay in the diagnosis of cutaneous malignant melanoma . A prospective study in 250 patients. Cancer 1991;68:2064-8.
15. Soon SL, Solomon AR Jr, Papadopoulos D, Murray DR, McAlpine B, Washington CV. Acral lentiginous melanoma mimicking benign disease: the Emory experience. J Am Acad Dermatol 2003;48:183-8.
16. Metzger S, Ellwanger U, Stroebel W, Schiebel U, Rassner G, Fleribeck G. Extent and consequences of physician delay in the diagnosis of acral melanoma. Melanoma Res 1998;8:181-6.
17. Franke W, Neumann NJ, Ruzicka T, Schulte KW. Plantar malignant melanoma: a challenge for early recognition. Melanoma Res 2000;10:571-6.
18. Phan A, Touzet S, Dalle S, Ronger-Savle S, Balme B, Thomas L. Acral lentiginous melanoma: a clinicoprognostic study of 126 cases. Br J Dermatol 2006;155:561-9.