Clinicopathological Study of Malignant Melanoma at Tertiary Care Centre

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ABSTRACT

Introduction: Malignant melanoma, which causes three fourth of all deaths related to skin cancer, is more common in Caucasian population compared to Asian population. There is no reliable information about malignant melanoma in Nepal hence an effort has been made to assess the clinical and pathological features of melanoma patients.

Methods: This was a retrospective hospital based study done in the department of Pathology. All cases of malignant melanoma diagnosed on biopsy during a period of 13 years were retrieved, reviewed and collated.

Results: We had 35 cases with age range from 15 to 84 years with the mean of 51.4 years and M: F of 1.3:1. The predominant site was lower extremities. Most cases were less than 3 cm. Majority of histologic subtypes were nodular melanoma 29 (82.8%) followed by mucosal lentiginous melanoma 3 (8.6%), superficial spreading melanoma 2 (5.7%) and acral lentiginous melanoma 1 (2.9%). Half (50%) of the excisional biopsies were at Clark's level IV and 75% were at high Breslow thickness.

Conclusions: The most frequent site in males and females were lower extremities and trunk respectively in contrast to Western studies where it is opposite. Nodular melanoma was the commonest histologic subtype while in other Asian studies and in Western studies majority were acral lentiginous melanoma and superficial spreading melanoma respectively.

Keywords: Breslow thickness; Clark's level; malignant melanoma; nodular melanoma.

INTRODUCTION

Malignant melanoma, which originates from the melanocytes, is an important disease entity as it causes majority (75%) of deaths related to skin cancer.¹ According to World Health Organization Cancer Facts in 2012, it was 15th and 16th most commonly diagnosed cancer in males and females respectively with worldwide incidence rate of 3.3 in males and 2.8 in females per lakh/year and it had a mortality rate of 0.9 in males and 0.6 in females per lakh/year.² Incidence rate of melanoma shows substantial variation worldwide with the incidence being highest in New Zealand and the lowest in Asian countries like China, India, Japan and

Singapore.^{3,4} In Asian countries, 11,000 and 10,000 cases of malignant melanoma were newly diagnosed in males and females respectively in 2012.²

The current study was done to determine the clinical and pathological characteristics of malignant melanoma diagnosed in patients in a medical college teaching hospital, Western Nepal and as per our knowledge this is the first study of melanoma in Nepal.

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METHODS

This was a cross sectional study conducted in the department of Pathology, Manipal Teaching Hospital, a tertiary care centre in western Nepal, from January 2001 to January 2014. Ethical approval was taken. Slides and data of all the cases of malignant melanoma diagnosed on histopathology during the study period were retrieved from the departmental data bank. All the slides were reviewed. Stains studied were H & E and Masson's Fontana in all the cases. The thickness of tumour was categorised by Breslow method and the level of tumour invasion was studied according to Clark's classification.^{5,6} The clinical and pathological characteristics like age, gender, anatomic sites, tumour size, histological subtypes, Breslow thickness, Clark's level of invasion, surgical margins and metastasis, if any, were noted and correlated.

RESULTS

There were 35 cases of malignant melanoma diagnosed

in the study period, of which 24 cases were excisional biopsies and 11 cases were incisional biopsies.

The age of the patients ranged from 15 to 84 years with a mean being 51.4 years (Table 1). There were 20 (57.1%) male and 15 (42.9%) female patients with male to female ratio 1.3:1. Among different age groups, 61-80 years was the largest comprising 14 (40%) cases. Among the males, majority (45%) were in the age group 61 – 80 years whereas in females, age groups 41 – 60 years and 61 – 80 years both consisted 5 (33.3%) cases each.

Among all the different sites of involvement, lower extremities 16 (45.7%) were the commonest site, followed by trunk 5 (14.3%) and upper extremities 4 (11.4%). Out of 16 cases of lower extremities, feet were involved in 13 cases (37.1%), including 9 cases on the sole and 4 cases on the great toes. Among the males, majority occurred in lower extremities 11 (55%) whereas trunk was the commonest site of occurrence for the females 4 (26.7%) (Table 1).

Table 1. Distribution of age groups and its correlation with gender and histological subtypes.								
Age group (years)	$N_{\rm L}$ (m)	F (n)	Histological subtypes					
	IVI (II)		*NM n (%)	†SSM n (%)	‡ALM n (%)	§MLM n (%)	Total n (%)	
<20	2	1	3 (8.6)	-	-	-	3 (8.6)	
21 – 40	4	3	6 (17.1)	-	-	1 (2.9)	7 (20)	
41 – 60	4	5	6 (17.1)	1 (2.9)	-	2 (5.7)	9 (25.7)	
61 – 80	9	5	12 (34.3)	1 (2.9)	1 (2.9)	-	14 (40)	
>81	1	1	2 (5.7)	-	-	-	2 (5.7)	
Total	20	15	29 (82.8)	2 (5.7)	1 (2.9)	3 (8.6)	35	

*NM - Nodular Melanoma, †SSM - Superficial Spreading Melanoma, ‡ALM - Acral Lentiginous Melanoma, §MLM - Mucosal Lentiginous Melanoma.

Table 2. Distribution of histological subtypes according to site and sex.									
Sites	NM* n=29		SSM \dagger n = 2		ALM \ddagger n = 1		MLM§ n=3		Total (n)
	M (n)	F(n)	M (n)	F (n)	M (n)	F (n)	M (n)	F (n)	rotar (n)
Upper extremities	2	2	-	-	-	-	-	-	4
Lower extremities	11	2	-	2	-	1	-	-	16
Nasal	2	1	-	-	-	-	-	-	3
Conjunctiva	-	1	-	-	-	-	-	-	1
Cheek	1	-	-	-	-	-	-	-	1
Post-auricular region	1	-	-	-	-	-	-	-	1
Oesophagus	1	-	-	-	-	-	-	-	1
Rectal polyp	-	-	-	-	-	-	1	1	2
Vaginal mass	-	-	-	-	-	-	-	1	1
Trunk	1	4	-	-	-	-	-	-	5
Total	19	10	-	2	-	1	1	2	35

*NM - Nodular Melanoma, †SSM - Superficial Spreading Melanoma, ‡ALM - Acral Lentiginous Melanoma, §MLM - Mucosal Lentiginous Melanoma.

Table 3. Distribu	ution of Clar	k's level, Breslow				
thickness, surgical	margins and n	netastatic sites.				
Particulars Frequency [n (%)]						
	I	0				
	II	0				
Clark's level	III	4 (16.7)				
	IV	12 (50)				
	V	8 (33.3)				
	Low risk	0				
Breslow thickness	Intermediate risk	6 (25)				
	High risk	18 (75)				
Surgioal Margina	Free	17 (70.8)				
Surgical wargins	Positive	7 (29.2)				
	Lymph node	8 (33.3)				
Metastatic sites	Breast	1 (4.2)				
	Thigh	1 (4.2)				

The size of the tumour in all 24 cases with excisional biopsies ranges from 0.2 to 7 cm with the mean of 2.1 cm. Twenty two (91.7%) cases were less than 3 cm in size (Figure 1). We had 2 cases with tumour size 5 cm and 7 cm from vagina and thigh respectively.⁷



In the study, nodular melanoma (NM) 29 (82.8%) was found to be the most encountered histological subtype followed by mucosal lentiginous melanoma (MLM) 3 (8.6%), superficial spreading melanoma (SSM) 2 (5.7%) and acral lentiginous melanoma (ALM) 1 (2.9%). Correlating with age groups, NM was found more common in the age group of 61 to 80 years comprising of 12 cases (Table 1).

In both males and females, NM was the predominant histologic subtype comprising of 19 (95%) cases and 10 (66.7%) cases respectively. Out of 29 cases of NM, the lower extremities were found to be the most frequent site 13 (44.8%), followed by 5 in trunk and 4 in upper extremities (Table 2).

Of the 24 cases of excisional biopsies, majority 18 (75%) were found to be in high risk (>1.5mm) and 6 (25%) cases in intermediate risk (0.76 -1.5mm) categories.

Level of tumour invasion was measured according to Clark's classification in all the 24 cases of excisional biopsies. Half of the cases 12 (50%) were of level IV at the time of diagnosis, while 8 (33.3%) were of level V and 4 (16.7%) were of level III. None of the lesions in this study were classified as melanoma in situ, level I and II (Table 3).

In majority of the cases 17 (70.8%), margins were surgically free. Among the total 24 cases of excisional biopsies, metastases were found in 10 (41.7%) cases. The predominant metastatic sites were regional lymph nodes 8 followed by 1 case each in breast and thigh (Table 3). Among the total 8 cases of lymph node metastases, 6 cases were male and 2 cases were females.

DISCUSSION

As higher incidence rates of malignant melanoma have been found in countries with a predominantly fair-skinned population, most studies show clinical and pathological characteristics of melanoma in these populations.⁸ In Asian countries the incidence rates are less than 1 per 100,000 in contrast to US where it is 173 per 100,000.⁹ No data on incidence of melanoma in Nepal were available except for only a few reported cases of melanoma in vagina, eyes and nasal cavity.^{7,10,11}

In the study conducted by Nagore E et al. in Spain, the total number of cases enrolled in the study was 1571 over a period of 18 years.⁸ But in the study conducted by Hui S K et al. in Hong Kong Chinese patients over a period of 12 years, the total number of cases was only 32.¹ Laishram RS et al., Deo SV et al. and Sharma K et al. reported 13, 20 and 72 cases from India in study periods of 5, 7 and 12 years respectively.¹²⁻¹⁴ Our study included 35 cases of malignant melanoma during a period of 13 years. Such huge differences in the number of cases between different studies were due to higher incidence rates in fair- skinned population.⁸

In the study by Hui SK et al., the age of the patients ranged from 23 to 86 years with the mean age of 57.6 years.¹ Similarly, in the study by Saxe N et al. most of the patients were in their fifties.¹⁵ In our study, the age of the patients ranged from 15 to 84 years with the mean of 51.4 years and the largest group was 61-80 years.

In the current study, there were 20 (57.1%) male and 15 (42.9%) female patients with male to female ratio of

1.3:1. The gender distribution found in our study was consistent with the studies in Australia, USA, South Africa and other Asian countries like India where male predominated unlike the European and Canadian studies where females were predominant.^{8,13,14} However, in 2 studies from Asia by Hui SK et al. in Hong Kong and by Chang et al. in Taiwan, there were slight female predominance with male to female ratio of 1:1.13. ^{1,16}

In present study, 16 (45.7%) cases were in lower extremities which included 13 (37.1%) cases in feet alone. Our finding matched with the study of Hui SK et al. among Hong Kong Chinese patients as well as with other Chinese and Indian studies.^{1,17,18} However in two studies from North India done by Deo et al. and by Sharma et al., scalp, face and eyes were the commonest site.^{13,14}

Correlating sites with gender, the commonest sites among males and females in the current study were lower extremities (55%) and trunk (26.7%) respectively. In the studies among Caucasian population, most common primary site of melanoma for male is upper back while in female it is the lower extremities.^{1,8,13} However, in the last few years, Nagore E et al. have observed an increase in cases of malignant melanoma in the trunk region and decrease in lower extremities.⁸ Authors hinted that the differences in the anatomical sites among Asians as compared to Caucasians may point to the different aetiological factors among different ethnic groups.¹

In the study by Hui SK et al., majority (60.9%) were less than 3 cm in size.¹ In our series, 22 (91.7%) cases of excisional biopsies had tumour size less than 3 cm at presentation.

In 1969, Clark et al., using a combination of clinical and pathological features, suggested that melanoma could be divided into three main subsets, namely NM, SSM and LMM. In 1975, Reed RJ added a fourth group, the ALM.¹⁹ However, this classification system has lost some credibility over time because the biological behaviour of these lesions is essentially unrelated to the morphological name applied to the lesion and the prognosis of melanoma is more related to Breslow's tumour thickness rather than the traditional classification system.¹

According to the traditional classification, usually about 10 -20 % of melanomas are difficult to be subcategorised. Another approach to the pathological classification of melanoma has been proposed by Barnhill. In his proposed system, melanomas were classified into two main categories viz., convention melanoma and other unusual variants.¹ However, the Clark's classification system is the one that is commonly encountered in the literature and most textbooks and was used in this study for the classification purpose.

In Caucasian population, the commonest histologic subtype was reported to be SSM (70%), followed by NM (15 - 30%) and lentiginous maligna melanoma (LMM) (<15%).^{1,3} In the several studies done in Taiwan, ALM was the most common subtype of melanoma.⁴ Hui SK et al. found melanoma in-situ (34%) as the commonest subtype followed by ALM (22%) and NM (16%).¹ Whereas in this study, NM was found to be the most common (82.8%) subtype of melanoma followed by MLM (8.6%), SSM (5.7%) and ALM (2.9%). In the current study, NM was found to be more common in the male gender and in the age group 61-80 years. Barnhill et al.²¹ also found NM to be more frequent in men, but most cases were between 50 - 60 years. In the Taiwanese study by Chen YJ et al. also, out of the 15 cases of NM, males were predominant, comprising of 11 cases.³

Considering only NM subtype, Chen YJ et al.³ from Taiwan reported that feet were the commonest site and Barnhill et al.²¹ reported that trunk and lower leg were the commonest sites in males and females respectively. In contrary, in the current study we found more predilections of NM for lower extremities in men and for trunk in females.

We had 1 case of 22 years female with xeroderma pigmentosum which is known to be associated with skin malignancies.

Information on level of tumour invasion based on Clark's classification was available in all 24 cases of excisional biopsies. Eleven cases of incisional biopsies in this series had gone to other centres for further treatment. In the studies done by Chen YJ et al. and Chang JWC et al. majority of the patients had lesions at level V and level III at the time of diagnosis.^{3,16} In the present study, majority (50%) of the patients were at Clark's level IV, followed by V and III.

In the study by Nagore E et al., malignant melanoma was grouped as thin melanoma when tumour thickness was <1mm and thick melanoma when it was >4 mm. More than 40% of the thin melanomas were encountered under 60 years of age whereas thick melanomas predominated in the elderly.⁸ In other Taiwanese study by Soong et al., 60% of the patients had tumour thickness of more than 2.5 mm and none had thin melanoma.⁴ In our study majority of the cases 18 (75%) were at Breslow high risk category including 10 cases with more than 4 mm thickness. We did not find any correlation between tumour thickness and age.

Metastases were encountered in only 10 cases at the time of diagnosis in this study. In contrast, Chen YJ

found majority of NM cases with metastases 12 (80%), while, in the study by Nagore et al., majority (79.9%) were non-metastasizing similar to this study.^{3,8} In the current study, lymph node was the most common site of metastasis as in other studies.^{3,8}

Wide local resection of the primary site along with removal of clinically normal and abnormal regional lymph nodes as well as distant metastases is the method of treatment.⁴ Adjuvant chemotherapy and immunotherapy are also suggested by different authors.³

As it is a hospital based study, it may not represent the population at large. Thus the under representation of low grade melanoma e.g., melanoma in situ, level I and level II etc, is likely.

CONCLUSIONS

In the current study, lower extremities and trunk were the commonest sites among males and females respectively in contrast to Western studies where it is opposite. Commonest type we had was NM followed by MLM while in other Asian studies commonest type was ALM followed by NM and in Western studies SSM was the commonest followed by NM.

More studies from other regions of the country as well as in the community are invited to identify the exact clinico-pathological profile and epidemiological distribution of malignant melanoma in this part of the world.

Conflict of Interest: None.

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