



A CLINICOPATHOLOGICAL STUDY OF MALIGNANT MELANOMA IN A TERTIARY CARE HOSPITAL.

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ABSTRACT:

Background: Malignant Melanoma (MM) is an aggressive and most common lethal tumour of melanocytic origin. It represents less than 5 % of all cutaneous malignancies and accounts for majority of skin cancer deaths. The aim is to determine the clinicopathological features of MM and find a correlation between clinical and epidemiological factors with the different histomorphological parameters of the melanocytic tumours.

Material And Methods: This study was carried out at Mahatma Gandhi Medical College, Jaipur, India from July 2022 to December 2022. 20 consecutive cases diagnosed histopathologically with or without IHC as MM were included in the study. Various histopathological parameters were studied which include cell shape, invasion (based on Clark's system), presence of pigment, mitotic activity and dermal lymphocytic infiltration. Histopathological reporting was done as per CAP protocol and AJCC recent guidelines for resected specimen.

Results: Out of the total cases, 13(65%) were cutaneous and 7(35%) were non cutaneous melanoma. The most common age group was sixth decade with female predominance. Among non-cutaneous melanomas, 4 were in anorectum, 2 in breast and 1 in bladder. The acral lentiginous type was the most common variety with foot being the most common region. Clarks level III and IV was the most common level of invasion which presented at stage T3.

Conclusion: Lower extremity was the most common site amongst cutaneous melanomas. Tumour in lower extremities was more related with higher chance of metastasis. Anorectum being the most common site amongst non-cutaneous melanomas, presented with metastasis to colon.

Keywords: Melanoma, Bladder, Breast, HMB45

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INTRODUCTION

Malignant Melanoma (MM) is an aggressive and most common lethal tumour of melanocytic origin. The large majority of melanomas are associated with sunlight exposure and thought to be due to UV radiation. It represents less than 5 % of all cutaneous malignancies and accounts for majority of skin cancer deaths [1,2].

In Asian countries incidence rate is commonly less than 1/100000 year [3]. According to World Health Organization, the cases of malignant melanoma are increasing faster than any other cancer worldwide [4]. Among MM, cutaneous type is most common, whereas non cutaneous is rare type.

The aim of the study was to determine the clinicopathological features of MM in a tertiary care hospital of Northwestern part of India to find a correlation between clinical and epidemiological factors with the different histomorphological parameters of the melanocytic tumours.

MATERIAL AND METHODS

The present study was an observational and cross-sectional study carried out prospectively in compliance with the protocol in the department of Pathology and Oncopathology, Mahatma Gandhi medical college and Hospital, Jaipur. The study was conducted for a period of 6 months from July 2022 to December 2022. 20 consecutive cases diagnosed histopathologically with or without IHC as MM were included in the study. Patient's clinical history

and other investigation details were retrieved from hospital records.

Gross and microscopic details were noted including tumour size, gross appearance etc. and various histopathological parameters of the tumour were evaluated by studying Hematoxylin/ eosin-stained sections prepared from FFPE (formalin fixed paraffin embedded) blocks. Parameters include cell shape, invasion (based on Clark's system), presence of pigment, mitotic activity and dermal lymphocytic infiltration. Histopathological reporting was done as per CAP protocol and AJCC recent guidelines for resected specimen. Trucut and incisional biopsies are examined and reported as per size of the tissue. The tumour thickness was measured from the most superficial layer of mucosal epithelium, ulcer base or granular layer of squamous mucosa to the deepest invasive tumour cell. Immunomarkers such as HMB 45, SOX 10, S100, panCk and Vimentin were used on tissue sections with doubtful morphology by using our institutional immunohistochemistry protocol of HRP polymerase system.

RESULTS

In the present study, 20 consecutive cases of Malignant Melanoma were included. The median age of the patients was 61 years. The patients predominantly included 13 females (65%) and the sex ratio is 1.85:1 (Table 1)

Table 1: Distribution of Malignant Melanoma cases as per Gender

AGE GROUP	MALE	FEMALE	TOTAL
0 – 20	0	0	0
21- 40	2	2	4
41- 60	0	6	6
61- 80	5	4	9
81- 100	0	1	1
TOTAL	7	13	20

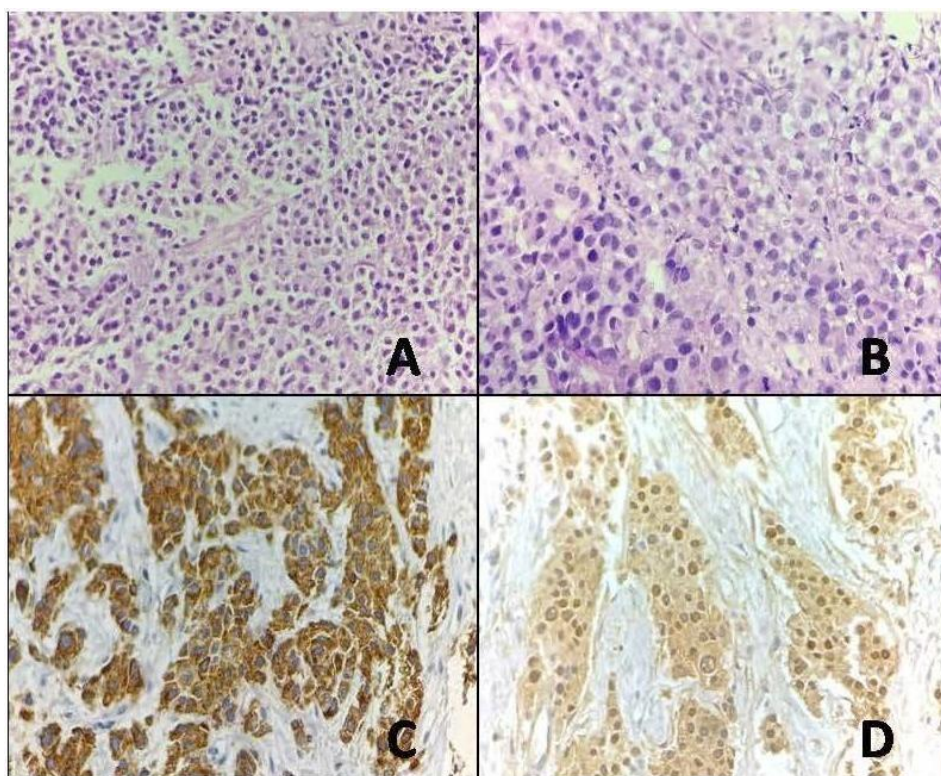


Figure 1: Histopathological and immunostaining results for Malignant Melanoma (A) Low power image shows tumour cells arranged in sheets and nest separated by fibrous septa. (H and E, x 100), (B) High Power image shows Epithelioid cells with high N:C, open up chromatin and prominent nucleoli. (H and E, x400) (C) HMB-45 shows diffuse strong positivity(x400), (D) S-100 shows diffuse positivity (x400).

Amongst the cutaneous Melanomas, 8 (61%) (Figure 1) were resected specimens and 5(38%) were either trucut or incisional biopsies. Most cases were found in the foot region (53%), showing a female preponderance (Table 2).

SITE	MALE	FEMALE	TOTAL
a) CUTANEOUS			
FOOT	3	4	7
THIGH	2	2	4
HEAD AND NECK	0	2	2
TOTAL	5	9	13
b) NONCUTANEOUS			
ANORECTUM	2	2	4
BLADDER	0	1	1
BREAST	0	2	1
TOTAL	2	5	7

Table 2: Distribution of Site of Malignant Melanoma according to gender

A single case of bladder melanoma was seen where tumour cells were seen infiltrating the deep muscle and was confirmed by HMB 45 and SOX 10. (Figure 2).

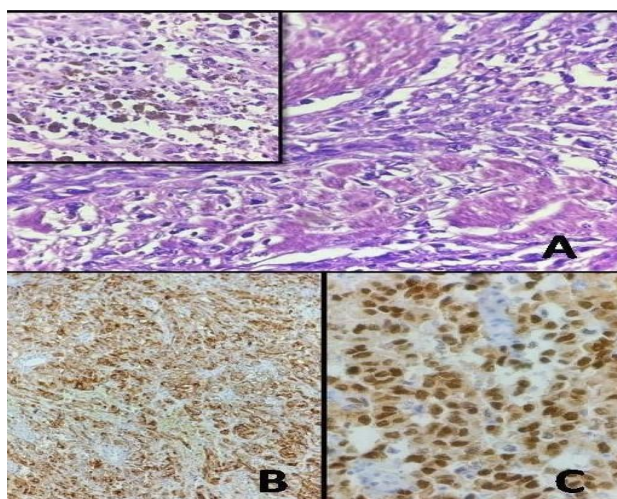


Figure 2: Histomorphological features of Melanoma in Bladder, (A) low power image shows tumour cells infiltrating the deep muscle. H and E (x400), Inset : High power image shows tumour cells with pigmentation , H and E (x400), (B) HMB-45 shows diffuse strong positivity (x100), (C) SOX-10 shows strong positivity (x400)

2 cases of breast melanoma were seen where one case shows spindle shaped cells arranged in sheets and fascicles showing granular, coarsely clumped

chromatin and conspicuous nucleoli. At places brownish pigment identified in tumour cells. It was confirmed by HMB 45 and S100. (Figure 3)

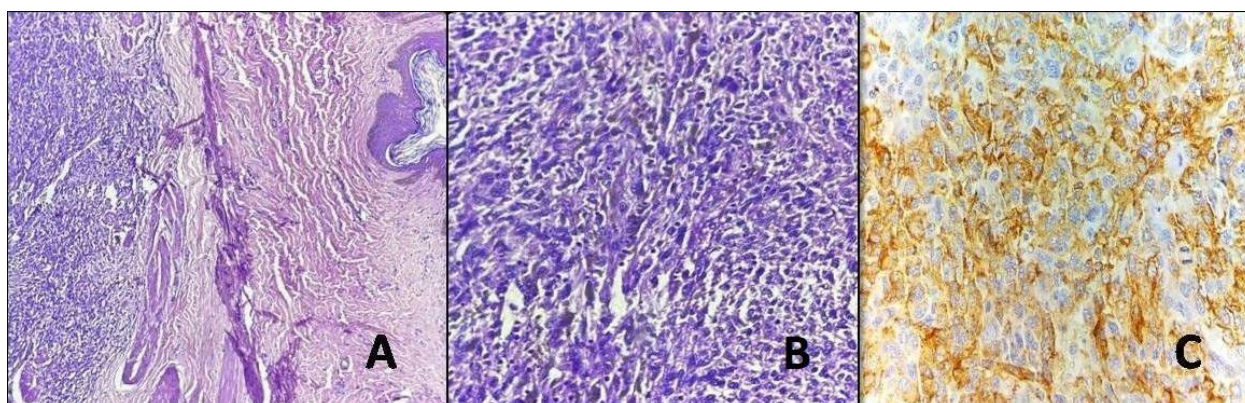


Figure 3: Histopathological findings in Melanoma in Breast. (A) Low Power Image shows Skin lined tissue showing tumour cells arranged in sheets in dermis. H and E (x100), (B) High power image shows spindle shaped cells arranged in fascicles with pigmentation. H and E (x400), (C) HMB-45 shows strong positivity(x400).

Amongst the different morphological types of melanoma, only in 10 cases (8 resected specimens and 2 biopsies) the type was identified. Most common was acral lentiginous with a total of 6 cases (60%). (Table 3)

SITE	Acral lentiginous	Superficial Spreading	Nodular	Total
FOOT	4	2	1	7
THIGH	1	1	0	2
HEAD AND NECK	1	0	0	1
TOTAL	6	3	1	10

Table 3: Distribution of Malignant Melanoma subtypes according to the site of involvement

Majority of the cases (19 cases) were melanotic melanoma, and only 1 case was reported as amelanotic melanoma.

Clarks grade III was reported as the most common grade which correlated with lower extremity. (Table 4)

SITE	I	II	III	IV	V	Total
FOOT	1	1	2	2	1	7
THIGH	0	1	0	0	1	2
HEAD	0	0	1	0	0	1
AND						
NECK						
TOTAL	1	2	3	2	2	10

Table 4: Distribution of Malignant Melanoma Clarks Level according to the site of involvement

Among the 8 resected specimens, 3 cases (37%) presented with surface ulceration. 2 cases (25%) showed microsatellite on histopathology. Mitotic figures were seen ranging from 1-2/10hpf to 10-12/10hpf. Lymphovascular space invasion was seen in majority of cases (75%). Neurotropism is not seen any of the cases. Tumour showed

maximum 20% Tumour infiltrating Lymphocytes. There were only 2 cases post neoadjuvant chemotherapy (NACT) and none of them showed tumour regression. Most common T stage was T3 which also correlated with lower extremity.(Table 5)

SITE	T1	T2	T3	T4	TOTAL
FOOT	1	1	3	1	6
THIGH	0	1	0	1	2
HEAD	0	0	0	0	0
AND					
NECK					
TOTAL	1	2	3	2	8

Table 5: Distribution of Malignant Melanoma pathological T Staging according to the site of involvement

Lymph node metastasis was found in 3 cases.

DISCUSSION

Melanoma is a cancer of melanocytes which is derived from pluripotent neural crest stem cells. It migrates to and involves the epidermis as well as to other extracutaneous pigment containing sites [5]. Melanoma has the highest mutational burden of any cancer partially attributed to UV induced DNA damage [6].

Global incidence rates of melanoma, are increasing over the years with United states alone reported 100,000 new cases of invasive melanoma in 2021 [7,8]. In India, cancer registry reports that the age specific incidence rate of cutaneous melanoma is less than 0.5 per 100,000 [9]. In our study, the highest incidence was observed to be in sixth to

seventh decade, with the median age be 61 years which was similar with the several studies [10 -12]. This study shows a female preponderance of melanoma which correlates with the study done by Castel T et al. [13] and is in discordance with Panda S et al. [10].In our study 65 % cases were of cutaneous melanoma which coincides with the findings in the study conducted by Sang yub Kim et al.[14] and Panda S et al. [10].

According to WHO Classification, cutaneous melanomas can be classified by its location, the amount of sun exposure at the affected site and the histopathological features of the tumour [15]. The four main subtypes are Lentigo Maligna Melanoma (LMM), Superficial spreading Melanoma (SSM),

acral lentiginous melanoma (ALM) and Nodular Melanoma (NM).

In our study most common site was found to be extremities where foot being the most common area (53%) followed by thigh (30%) and in non-cutaneous location Anorectum (57%) being the most common site which correlated with the results published by Castel T. et al. [13] and Bajpai J et al. [16].

Lower Extremities is the most common site of involvement in males while trunk is most common in females seen in studies conducted by Thapa S. et al. [12] and Vayer A. et al. [17].

In Asian Population, acral lentiginous melanoma is the most common subtype and is not associated with UV radiations per the study done by Sang yubkim et al. [14] and Lee et al. [18] which also correlated with our study which shows 60 % cases of acral lentiginous type and only 30% and 10% cases of superficial spreading and nodular types respectively with acral lentiginous type commonly seen in the lower extremities mainly foot (66% cases). Our study was in discordance with Shah N et al. [19] which showed only 17% Cases of Acral lentiginous type among cutaneous melanomas.

In our study Foot and thigh region showed the highest T staging but nothing can be concluded as there was only 1 case each. Metastasis to regional lymph nodes has significant therapeutic and prognostic implications for melanoma patients [20]. The probability of lymph node metastasis is affected by factors like tumor thickness and depth of invasion by neoplastic cells [21,22]. The most common site of metastasis includes inguinal lymph node, lung, liver and intestine.

In our study Inguinal lymph node was the most common site of metastasis with one case showing 13/17 positive inguinal lymph node and was given T4a staging involving foot. Only 1 case showed metastasis to ankle and was reported as T4NxM1a where the primary lesion was in the thigh showing ulceration. The prognostic factors in primary skin melanoma were studied by Clark and Breslow who observed that tumour thickness was an important indicator of behaviour. In our study majority of cases presented with Clarks level III which inconsistent with earlier studies done by Panda S et al [10] and Mukhopadhyay et al. [11].

Extracutaneous Melanomas or Mucosal Melanomas are extremely rare and shows a poor prognostic type of malignant melanoma. They are seen in the locations such as nasopharynx, genitourinary, anorectum and GI tract.

These patients show less than 25% five-year survival rate and various genomic studies have supported with the fact that UV light plays a very little role in their carcinogenesis.

In our study we found 4 cases (57%) in anorectum, 2 cases (28%) in breast and one case (14%) of bladder melanoma was seen.

Anorectal melanomas constitute only 0.5-4% of all anorectal malignancies and less than 1% of all melanomas [23,24]. In our study out of the 4 cases, 2 cases show metastasis to colon and both these cases were seen in male. Single case shows amelanotic melanoma in which there is a decreased or null presence of melanin due to the loss of pigment in tumour evolution. This case was therefore confirmed by HMB 45 staining.

A single case of Primary Melanoma of bladder was seen which was further confirmed on IHC. Primary melanoma of urinary bladder is rare and only 39 cases are reported worldwide [25].

Two cases of Primary melanoma of breast were seen. Primary melanoma in breast is very rare and often diagnosed as poorly differentiated breast carcinoma [26]. In the other case the histomorphology showed high grade malignant spindle cell tumour which on IHC was confirmed as Melanoma.

Apart from histological features, majority cases of melanoma require IHC to be performed to confirm it. In such scenario, in our setup we do S100, HMB45 and SOX 10. Messina et al. [27] reported S-100 to be most sensitive and HMB-45 to be too insensitive. However, S-100 positivity was also demonstrated in benign nevi, dendritic reticulum cells and Langerhans cells in addition to melanoma cells, suggesting less than optimal specificity of this technique. HMB-45 is a widely used immunohistochemical stain for detection of primary as well as metastatic melanoma [28]. Presumably, this method uses monoclonal antibodies to a glycoprotein that is present in premelanosomes. HMB-45 is considered to be a more reliable and specific marker of melanoma cells because of higher clarity and minimal background staining. Gibbs et al. [29] concluded that combination of multiple levels of H & E sections in conjunction with S-100 and HMB-45 immunohistochemical staining dramatically increases the overall diagnostic sensitivity.

Sry-related HMG-Box gene 10 (SOX10) is a nuclear transcription factor that plays an important role in melanocytic cell differentiation. Studies showed that S100 and SOX10 remain the most sensitive markers for melanocytic tumours [30-33]. HMB-45, tyrosinase, and SOX10, alongside the Ki67 index, can aid in the distinction between benign and malignant melanocytic tumors [31, 32]. SOX10 is also a sensitive marker for desmoplastic MMs [33]. SOX10 correlates with the rate of lymph node metastasis, a double positivity of MMs for SOX10/SOX11 might be used as an indicator of the

presence of tumor cells in lymphatic and systemic circulation [34].

Among the histomorphological parameters studied, it is shown that the cases showing high mitotic count were also seen to have a high clarks grading and lymphovascular invasion. The limitations of the study consist in the relatively small number of examined cases, so for any conclusion large sample size should be studied.

CONCLUSION

In the present study females were most commonly affected and lower extremity was the most common site amongst cutaneous melanomas. Majority of cases were of acral lentiginous type with Clarks grade III and IV and presented at stage T3. Tumour in lower extremities were more related with higher chance of metastasis. Anorectum being the most common site amongst non-cutaneous melanomas, presented with metastasis to colon. Very rare case of breast melanoma was seen which can only be confirmed by HMB 45.

CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interest to disclose.

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