Original Article

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Melanocytic Lesions- A Hospital-based Descriptive Study from Central Kerala, India

Pathology Section

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ABSTRACT

Introduction: Malignant melanoma is a tumour of melanocytic origin. There is considerable geographic variation in the incidence of melanocytic lesions and are related to exposure to sunlight and susceptibility of the population. Descriptive and statistical studies of melanocytic lesions are few among Indian populations.

Aim: To describe and categorise melanocytic lesions, analyse their histological features and form evidence based data applicable to Indian population.

Materials and Methods: The present descriptive study was conducted in Department of Pathology in a tertiary care centre in central Kerala, India from August 2013 to July 2016. Total duration of the study was 36 months starting from 2013 August to 2016 July. Melanocytic lesions received in Pathology Department for the study period were analysed. Data including age, gender, signs and symptoms, anatomical site, clinical and gross photographs were analysed. For each case, gross and histopathological examination were done. In some cases histopathological study alone was not diagnostic, so Immunohistochemistry (IHC) including Human Melanoma Black (HBM)-45 and Melan-A were conducted to establish melanocytic differentiation. Final statistical analysis was done by frequency measurements and cross tabulation using Statistical Package for the Social Sciences (SPSS) software version 17.0.

Results: Total sample size was 57, among which 44 cases were from cutaneous sites (27 benign and 17 malignant) and 13 were from mucosal sites (2 benign and 11 malignant). Most of the cases were from above 60 years age group (35%). Anatomically, majority of cutaneous melanomas were from lower limb {15 (88.2%)} and majority of mucosal melanomas were from upper gastrointestinal tract {5 (38.4%)}. Although prominent nucleoli are said to be characteristic feature of melanomas, 8 out of the 28 total cases of melanomas had inconspicuous nucleoli (28.5%). When cell morphology of melanomas was studied, majority of cases had oval cells 10 (35.7%). It was also found that there was a significant correlation between spindle cell morphology and absence of pigment in melanomas (p-value=0.004). There was no association between mitosis in melanomas and vertical tumour diameter (p-value=0.1837).

Conclusion: A female predominance was observed and the commonly effected age group was above 60 years. Intradermal nevi were the major benign melanocytic lesion, while the common site was lower limb among cutaneous melanomas and upper gastrointestinal tract among mucosal melanomas. A positive association between absence of pigment in malignant melanomas and predominance of spindle cells was found.

Keywords: Cutaneous, Melanin, Melanoma, Mucosal, Nevus

INTRODUCTION

Melanocyte precursors arise from neural crest cells and migrate to skin during embryonic development. In postnatal skin, melanocyte progenitors are mainly located in the bulge region of hair follicle. Upon each hair cycle, melanocyte precursors differentiate and migrate into hair bulbs to become fully matured melanocytes determining animal hair and skin colour [1].

Melanocytic lesions are of primarily of importance because of malignant melanoma which is the single most common potentially lethal neoplasm of the skin. Nevi and other pigmented lesions are occasionally of cosmetic significance. Moreover, worldwide, the incidence of melanoma has risen dramatically over the last 50 years [2,3]. Prevalence of melanoma is higher among white population which can be attributed to their habit of regular sunbathing and genetic susceptibility. Thus, global incidence is highest in Australian tropics (ASR=34.9: 100,000 cases per year), but is low in most other tropical countries with their less susceptible population [2]. Although Asian countries especially India were considered as low incidence area (ASR=4:100,000 cases per year), recent studies question this data [4].

Descriptive and statistical studies of melanocytic lesions are few in Indian population. Besides this, the worldwide statistics do not match with that seen in India. Melanoma is disproportionately reported among fair skinned Caucasian population. Compared to fairer-skinned people, Ultraviolet B (UVB) radiation through the epidermis is diminished by approximately 50% in darker skinned people [2,3]. Studies from India show lower limb as the most common site for melanoma and most commonly affected age group is 6th decade. Among Caucasian populations, melanoma is more frequently reported on the back and shoulders of men and the lower limbs of women. Most common age group affected is 7th to 8th decade [2-5].

It can be difficult at times to categorise melanocytic lesions as benign or malignant as some benign melanocytic entities can mimic melanoma histologically. Some benign cases even show unusual features such as asymmetry of the silhouette, excessive junctional activity, mild cellular pleomorphism, deep extension into subcutis and mitosis [6]. So, systematic and detailed analysis of melanocytic lesions is necessary in order to avoid potential errors. Therefore, it is important to approach all melanocytic lesions in ritualistic and consistent manner to avoid potential diagnostic errors [6].

The present study intended to analyse the melanocytic lesions according to their type, anatomical site, age of presentation and sex ratio placing particular emphasis on histological features and risk of aggressive behaviour and form an evidence based data that is applicable to our population.

MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted in the Department of Pathology at tertiary care centre, Government Medical College, Thrissur, Kerala, India. Both retrospective and prospective data collection was done and systematic analysis of the data was

done at the end of study period. The entire research procedure was in accordance with the ethical standards of the responsible committee on human experimentation. Informed consents were taken from the participants. Institutional Ethical Committee approval was taken (01/02/2012).

Inclusion criteria: Biopsies of melanocytic lesions anywhere in the body, including skin and mucus membrane submitted to Department of Pathology for three consecutive years were included in the study.

Exclusion criteria: Specimens for which proper patient and clinical data were not available, melanomas which already had undergone chemotherapy, non availability of tissue blocks for study were excluded from the study.

Out of the 69 cases considered, only 57 satisfied the inclusion criteria. Among these nine were retrospective cases collected from September 2012 to July 2013. For prospective cases for which fresh specimen were available, careful gross examination was done. For the retrospective cases details of gross specimen were collected from surgical notes in medical records and the request forms.

Study Procedure

Clinical data was collected for each case in a proforma: age, gender, signs, symptoms, anatomical site of lesion. Clinical and gross photographs of relevant cases were taken with good quality digital camera.

Cases for which only paraffin embedded tissue blocks were available, were studied by cutting 4-µm sections and staining with Hematoxylin and Eosin stain (H&E). For those cases which were studied prospectively, the biopsies were fixed in 10% formalin. Paraffin embedded tissue blocks were prepared and were cut into 4-µm sections and stained with H&E. Histopathological data was collected and analysis was done.

In the first step lesions were classified into cutaneous and mucosal lesions broadly. Both categories were further divided into benign and malignant lesions after detailed microscopic examination. Among the cutaneous lesions, nevi were subclassified according to the site of melanocytic proliferation as junctional compound and intradermal nevi [7].

Individual lesions were evaluated for the presence of maturation, and pigment within the lesion. Individual cell morphology was studied. They were classified as round, oval, spindle or combinations of the same. Nuclear chromatin, nuclear membrane and presence of nucleoli were also noted. Those lesions which had mitosis were graded according to degree of mitosis. For larger tumours, one full breadth of dermal tumour mass was scanned. For smaller tumours, the entire dermal tumour mass was scanned. Mitotic figures in tumour cells were tallied for each high power field. Finally the average counts per high power field were transformed into mitotic rate per square millimetre. Mitotic rate was categorised in 3 groups as follows: <1/mm^2, 1-4/mm^2, >4/mm^2 [8].

Melanomas were also classified according to their growth pattern as radial growth phase, vertical growth phase and nodular growth. In those cases where individual cell morphology was obscured due to dense melanin pigment, bleaching was done to reveal cell morphology. For five cases for which histopathological study alone was not diagnostic immunohistochemical study including Human Melanoma Black (HBM)-45 and Melan-A was done to establish melanocytic differentiation.

STATISTICAL ANALYSIS

The results obtained along with patient details were entered in Microsoft Excel and further analysis done using frequency measurements and cross tabulations using Statistical package for Social Science (SPSS) software version 17.0 where indicated. Chi-square test was applied to check the association between male gender and degree of mitosis in melanomas. Association between spindle cell morphology and amelanotic melanoma was tested using Fishers-Exact test and calculating odd's ratio.

RESULTS

Out of the 57 cases, 44 were from cutaneous sites while 13 belonged to mucosal sites. Demographic data of both cutaneous and mucosal lesions was analysed. Majority of cases in cutaneous lesions were in the age group above 60 years. Among both category, females were predominant. Considering all cases together majority of cases were from head and neck region [Table/Fig-1-3].

Age (years)	Cutaneous lesions (44)		Mucosal lesions (13)	
	Male	Female	Male	Female
≤20	1	5	0	0
21-40	4	8	3	2
41-60	4	7	1	3
Above 60	7	8	2	2
Total	16 (36.4%)	28 (63.6%)	6 (46.2%)	7 (53.8%)

[Table/Fig-1]: Age and gender distribution of cases.

Signs and symptoms	Cutaneous lesions	Mucosal lesions
Removal for cosmetic purpose	12	2
Increase in the size of pre-existing lesion	32	
Swelling and ulceration		5
Dysphagia and vomiting		2
Difficulty in breathing		2
Bleeding per rectum		1
Metastatic work-up*		1

[Table/Fig-2]: Signs and symptoms associated with the melanomas.
*Patient presented with a lesion in oral cavity. Primary site was revealed after further investigations

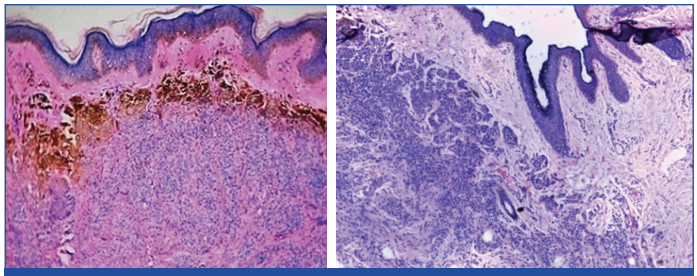
Anatomical location	Frequency
Head and neck	23 (40.35%)
Trunk	4 (7.01%)
Upper limb	2 (3.50%)
Lower limb	15 (26.31%)
Respiratory tract	2 (3.50%)
Upper GIT	5 (8.77%)
Lower GIT	1 (1.75%)
Genital system	2 (3.50%)
Conjunctiva	3 (5.26%)

[Table/Fig-3]: Anatomical distribution of the melanocytic lesions.

Out of the 44 cases, 27 were benign lesions and 17 were malignant. All the 27 benign cases were melanocytic nevi. Melanocytic nevi were again classified into junctional nevus, intradermal nevus and compound nevus. They were assessed for characteristic of pigment distribution, presence of mitosis, nesting pattern and maturation [Table/Fig-4-6].

Melanocytic nevus	n (%)	Pigment distribution				Mitosis		Maturation	
		Upper	Middle	Lower	Throughout	Yes	No	Yes	No
Junctional	1 (3.7%)	NA	NA	NA	NA	0	1	NA	NA
Compound	5 (18.5%)	4	0	0	1	1	4	4	1
Intradermal	21 (77.7%)	20	0	0	1	1	20	19	2
Total	27 (100)	24	0	0	2	2	25	23,88.4%	3,11.5%

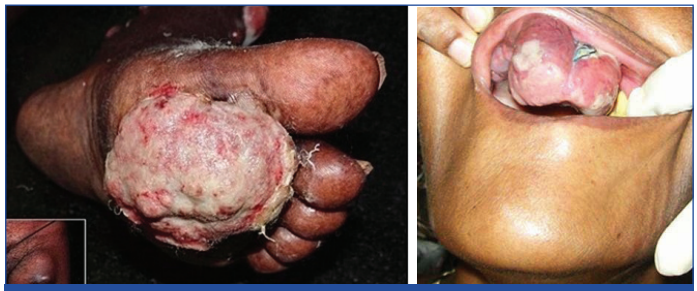
[Table/Fig-4]: Pigment distribution, mitosis and maturation in the 27 melanocytic nevi.
Jumctional nevus can not be assessed for maturation. So one case is excluded (n=26)



[Table/Fig-5]: Intradermal nevus showing pigment predominantly in the upper part (H&E, X100). **[Table/Fig-6]:** Nevus showing nesting of melanocytes (H&E, X100). (Images from left to right)

Anatomical distribution of cutaneous melanomas were, out of the 17 cutaneous melanoma cases 15 were from lower limb while head and neck region and upper limb constituted one case each. Four cases of cutaneous melanomas presented with inconspicuous nucleoli while the rest 13 cases had large prominent nucleoli. One case was found to be amelanotic [Table/Fig-7]. Growth pattern in melanomas were, 14 cases had vertical and horizontal growth pattern, three presented with nodular growth pattern while none had radial growth pattern.

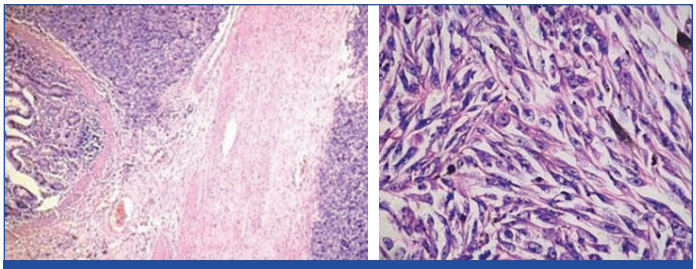
Analysing the mucosal lesions separately, only two were found to be benign in contrast to cutaneous lesions where benign cases predominated. Mucosal melanomas were studied separately for their anatomical distribution where five cases were from upper gastrointestinal tract, respiratory tract and genital system had two cases each, conjunctiva and lower Gastrointestinal Tract (GIT) also had one case each [Table/Fig-8-11]. Three out of 11 mucosal melanomas were amelanotic. Predominant cases showed either oval or spindle cell morphology [Table/Fig-12]. Three showed both oval and spindle cells. None of them showed perfectly round cells.



[Table/Fig-7]: Clinical photograph of a cutaneous amelanotic melanoma mimicking squamous cell carcinoma and its inguinal metastasis.
[Table/Fig-8]: Malignant melanoma presented as polypoidal lesion in oral cavity. (Images from left to right)

[Table/Fig-9]: Barium swallow test of an oesophageal melanoma showing filling defect **[Table/Fig-10]:** Cutaneous melanoma metastasis to small intestine clinically mistaken as Gastrointestinal Stromal Tumour (GIST). (Images from left to right)

Considering cutaneous and mucosal lesions together, there were 28 cases of malignant melanomas. They were studied for the presence and number of mitosis. Fifteen cases had >4 mitosis/mm^2 while ten cases had 1-4 mitosis/mm^2 and three had no mitosis at all. Among males, nine (60%) of them showed high degree of mitosis as against six (40%) females. Chi-square test showed no statistical significance between male gender and degree of mitosis (p-value 0.256) and the odds ratio was 2.400. Out of the 17 cases of cutaneous melanomas,



[Table/Fig-11]: Photomicrography of [Table/Fig-10] showing normal mucosa and all other layers showing metastatic melanoma cells (H&E, X 40).
[Table/Fig-12]: Melanoma showing cells with spindle cell morphology (H&E X400). (Images from left to right)

15 (88.2%) were acral lentigenous mealanomas in which 14 (82.3%) were from lower limb. Present study also showed a value which was comparable to the above data (5.8%).

Comparison was done between mitosis and tumour vertical diameter [Table/Fig-13]. Fishers-Exact test value established no significant association with p-value=0.1837.

Tumour vertical diameter	Number of mitosis			Total	p-value
	Low	High	Number of mitosis		
<1 cm	0	0	1, 33.3%	1, 3.6%	0.1837
1-5 cm	8, 80.0%	8, 53.3%	1, 33.3%	17, 60.7%	
>5-10 cm	1, 10.0%	6, 40.0%	1, 33.3%	8, 28.6%	
>10 cm	1, 10.0%	1, 6.7%	0	2, 7.1%	
Total	10, 100%	15, 100%	3, 100%	28,100%	

[Table/Fig-13]: Relation between tumour vertical diameter and mitosis.

Amelanotic melanomas were evaluated for cell morphology and there was increased incidence of spindle cell morphology among amelanotic melanomas. Applying Fishers-Exact test p-value was 0.004 with odds ratio 0.022189 revealed significant correlation between spindle cell morphology and amelanotic melanomas [Table/Fig-14]. Total 24 (88.8%) cases of benign nevi showed heavier melanin distribution in the upper part of dermis and only two case showed uniform distribution throughout the lesion.

Pigment	Cell morphology				Total	p-value	OR
	Oval	Spindle	Round and oval	Oval and spindle			
Absent	1, 10%	3, 75%	0	0	4, 14.3%	0.004	0.022189
Present	9, 90%	1, 25%	5, 100%	9, 100%	24, 85.7%		
Total	10, 100%	4, 100%	5,100%	9,100%	28, 100%		

[Table/Fig-14]: Correlation between absence of pigment and spindle cell morphology.

DISCUSSION

Melanocytic lesions will be one of the important topics of interest in upcoming years because of recent increase in incidence of melanoma even in countries like India which was considered to be low prevalent area [2-4]. The present study conducted in a tertiary care centre in southern India, aimed to describe and categorise melanocytic lesions, analyse their histological features and form an evidence based data applicable to Indian population. Total 57 cases of melanocytic lesions were included in the study among which 44 were from cutaneous sites and 13 were from mucosal sites. Incidence of malignancy among cutaneous melanocytic lesions was 17 (39%). This was high compared to other studies where proportion of malignant cases where around 14-15% among cutaneous lesions [9,10]. This can be probably due to higher frequency of excision of suspected malignant lesions. All cases of cutaneous melanocytic nevi in this study had a symmetrical silhouette both on gross and histological examination. Majority of them (66.6%) had gross horizontal tumour diameter less than 1 cm. These two findings are comparable to that of several other studies where symmetrical silhouette and small gross horizontal

diameter were found to be characteristic of benign melanocytic lesions [6-11].

In the present study, 77.7% cases of benign melanocytic nevi were intradermal nevi. Among these, excluding a single case of junctional nevi, all showed the particular arrangement of cells called maturation which refered to gradual and progressive change in nest architecture and melanocyte cytology [7]. Similar findings were reported in other studies also [12,13]. In this study, 24 (88.8%) cases of benign nevi showed heavier melanin distribution in the upper part of dermis and only two case showed uniform distribution throughout the lesion. This is similar to data obtained from other studies [6,14]. Available data on mitosis in melanocytic nevi shows wide variation, ranging from 0.95% in study conducted by Ruhoy SM et al., to 19.5% by Glatz K et al., [15,16]. In the present study, a total of 2 from 26 (7.7%) cases were found to have one or more mitotic figures. This is similar as that of study conducted by O'Rourke EA et al., who reported that out of 1041 benign melanocytic nevi 7.9% cases presented with mitotic figures [17].

Out of the 17 cases of cutaneous melanomas, 15 (88.2%) were acral lentigenous mealanomas in which 14 (82.3%) were from lower limb. Previous studies in Asian population also showed comparable results [18,19]. Melanomas characterised by complete or partial absence of pigment come under amelanotic melanomas and it account for 2-8% of all cutaneous melanomas as proven in previous studies [20-22]. Present study also showed a value which was comparable to the above data (5.8%).

In the present study, the total number of melanomas including both cutaneous and mucosal lesions was 28. Among the 28 cases gender distribution was equal. This data does not match with that of previous studies which shows, the definite male propensity [23,24]. Reason for this discrepancy can be the small sample size in this study. Out of the 28 cases of melanomas, three had no obvious mitosis (10.7%). Among the 25 cases which had mitosis, 15 had high mitotic rate (53.6%) and 10 had low mitotic rate (35.7%). Previous studies showed a positive correlation between high mitosis and male gender, but the present study failed to establish this results [7,23].

In this study, 11 (39.28%) out of the 28 melanomas were from mucosal site including head and neck, GIT and genital regions. This is comparatively a high proportion when previous studies are considered [25,26]. But there are studies which prove, the high incidence of mucosal melanomas in blacks (11.8%) compared to white population (1.3%). This is possibly because of the much lower incidence of cutaneous melanomas in black population [27]. Out of the 11 mucosal melanomas majority cases 5 (45.45%) were from head and neck region. This data is in accordance with previous studies [25-27].

Present study proves the proportion of amelanotic cases among cutaneous and mucosal melanomas shows wide variation ranging from 5.8% among cutaneous sites to 27.3% in mucosal sites. Several recent studies report more cases of amelanotic melanomas from mucosal sites than cutaneous sites [28-30]. As proven in previous studies, presence of melanoblasts in mucosal sites is established in the present study also with one case of oesophageal melanoma which was investigated and found to be primary in origin [28-31]. Recent studies stated that majority of GIT melanomas are metastatic and among them the favourable site being small intestine [32,33]. The present study also agrees with this data as 2 out of the 5 cases of upper gastrointestinal tract melanomas were secondaries from melanoma lower limb.

Limitation(s)

Since the number of lesions available for the study is few, conclusion made can only be provisional and a study including a larger number may be necessary to establish the profile of melanocytic lesions applicable to our population.

CONCLUSION(S)

Intradermal nevi were the major benign melanocytic lesion and they showed melanin pigment distribution mainly in the upper part of lesion. Seperate analysis of melanomas showed that lower limb was the most commonly affected site among cutaneous melanomas and upper gastrointestinal tract among mucosal melanomas. Although previous studies show definite male propensity for melanomas, this study showed equal gender distribution. Present study established no association between male gender and high degree of mitosis which was in disparity with previous studies. Study also showed a positive correlation between absence of pigment in malignant melanomas and predominance of spindle cells with p-value 0.004737 and odds ratio 0.022189.

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