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A Clinicopathologic Study of Melanocytic Neoplasms

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Abstract: This study reports baseline information about melanocytic neoplasms in TUTH. The objective was to study the histological spectrum of melanocytic nevi and melanoma, and to make a clinicohistopathological correlation. 50 consecutive cases of melanocytic neoplasms were studied from December 2010 to December 2011.Of the 50 cases, 12 (24%) were malignant melanoma and 38 (76%) were melanocytic nevi. Cutaneous melanocytic nevi was the commonest, 30/38, (79%) followed by 8/38 (21%) conjunctival nevi. Head and neck was the commonest site (25/38) and the mean age at presentation was 32.66 ±16.19 years, the female to male ratio being 5.3:1.In melanoma, 4 (33%) were extracutaneous, of the cutaneous, 2 (17%) were acral lentiginous, and 6 (50%) were nodular. Mean age was 50 ± 16.99 years with an equal female to male ratio. Commonest site was extremities (6/8) in cutaneous and choroid in extracutaneous (2/4) lesions. Concordance between clinical and histopathological diagnosis were found in 30/50 (60%) cases. Melanocytic nevi are quite common in females, melanoma is rare, affecting men and women equally. In our context melanoma likely represents a sporadic disorder. Difference from the western societies is the common occurrence of nodular melanoma here and the topographical distribution.

Keywords: Cutaneous and Extracutaneous, Clinicopathologic, Melanocytic Neoplasms

INTRODUCTION

Melanocytic nevi are important primarily because of their histogenic relation to cutaneous melanoma [1]. Rarely melanomas can arise at noncutaneous sites such as ocular, meningeal, and mucosal melanomas. Extra cutaneous melanomas (ECM) seem to be biologically more aggressive than most Cutaneous melanomas (CM) [2].

To the best of our knowledge, the clinicopathologic features of these lesions, in Nepalese have still not been studied. Therefore with the aim to delineate their features and demographic characteristics in the Nepalese population, all histopathologically diagnosed cases of melanocytic neoplasms received at the Department of Pathology, at our hospital were reviewed over a one year period.

MATERIALS AND METHODS

A total of 50 biopsy specimens from 50 patients were included from the histopathology section of the department of Pathology at our hospital, over a period of one year from December 2010 to November 2011. All histology specimens were fixed in 10% formalin, paraffin blocks cut and stained with conventional hematoxylin and eosin and the data of the patients obtained from hospital records. Depending upon the diagnosis the following parameters were recorded for comparison:

For melanocytic neoplasm: presentation (as a mass or an ulcer)**,** size of the lesion**,** pigmentation and site.

For melanocytic nevi: Component (compound or dermal)**,** junctional activity**,** cell type (epithelioid, spindle cell)**,** mitosis**,** pigmentation**,** lamellar fibrosis**,** concentric eosinophilic fibrosis**,** dysplasia**,** senescence**,** neurotization**,** adnexal involvement**,** tumor infiltrating lymphocytes**,** and epidermis (normal, atrophic or with both normal and atrophic areas).

For Malignant Melanoma: Histologic type (superficial spreading, nodular, acral lentiginous melanoma and lentigo maligna melanoma), when the tumor had mixed features, classified according to the prevailing type, levels of invasion categorized following the guidelines of Clark, thickness in millimeters measured according to the method by Breslow, inflammatory reaction categorized by comparing the numbers of the inflammatory cells (lymphocytes) within and adjacent

to the periphery of the lesion with the surrounding tissues, mitotic activity was reported as low (<5/10 hpf) and high (>5/10 hpf) [3], growth phase, junctional activity and pagetoid spread (in case of cutaneous melanoma), necrosis, desmoplasia and tumor infiltrating lymphocytes (brisk, non-brisk or none).

RESULTS

Of the total of 6249 biopsy specimens received during the period from December 2010 to November 2011, there were a total of 50 specimens of melanocytic neoplasms (50/6249) (0.8%).The clinical diagnoses of the patients were noted and the histopathological parameters of the characteristic lesions were studied at the time of presentation.

The mean age of the patients was 36.82+17.85 years. There were 38 females, and 12 males. The female to male ratio was 3.2:1. The largest number of patients were in the age range, 20-39 {22(44%)}, and the least number of patients were in the age range, > 60 {7(14%)}.Out of a total of 50 cases, 12 (24%) were malignant melanoma and 38(76%) were melanocytic nevi. The total number of cases clinically diagnosed as nevi were 23 (46%), as malignant melanoma were 16 (32%), as other cutaneous malignancies were 7 (14%), as papilloma were 2 (4%) and as cutaneous tuberculosis were 2 (4%).Out of a total of 50 cases, concordances in the clinical and histopathological diagnosis were found in 30 (60%) cases and discordance was found in 20 (40%) cases (Table 1).

Table 1: Characteristics of melanocytic neoplasms

Properties	**Nevus**	**Melanoma**
Age in years(mean+SD)	32.66 +16.19	50 + 16.99
Age in years(median)	31.50	52.50
Size in mm(mean+SD)	9.82 + 12.69	17.46 + 11.57
Size in mm(median)	7.50	15.00
Sex		
Male	6/38	6/12
Female	32/38	6/12
Site		
Cutaneous	**30/38**	**8/12**
Head and neck	25/38	1/12
Trunk	4/38	1/12
Extremities	1/38	6/12
Extracutaneous	**8/38**	**4/12**
Choroid	0/38	2/12
Conjunctiva	8/38	1/12
Nasal cavity	0/38	1/12
Presentation		
Mass	14/38	7/12
Ulcer	0/38	5/12
Pigmentation	38/38	8/12

Out of the total of 12 cases of malignant melanoma, highest number of cases {5 (42%)} were within the age range 40-59, while the least number of patients {3(25%} were within the age range 20-39. Out of 12 cases of melanoma, 4 were extracutaneous and 8 were cutaneous. Out of the 8 cases of cutaneous melanoma,2 (16.7%) were of the acral lentiginous type, one of them among which also showed features of regression (Figures 1, 2, 3) and 6 (50%) were of the nodular type (Figures.4,5).

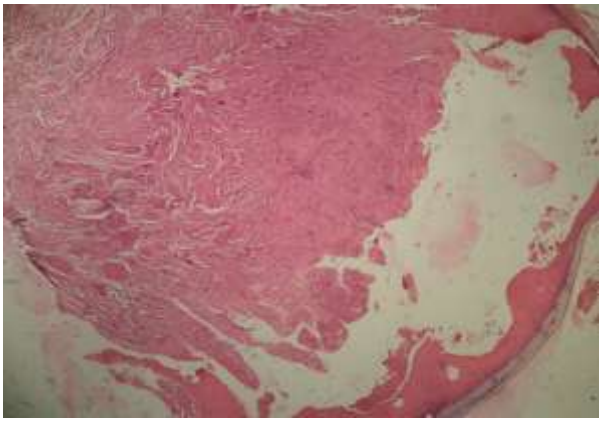

Fig-1: Acral lentiginous melanoma (ALM) with features of regression; x400 H&E

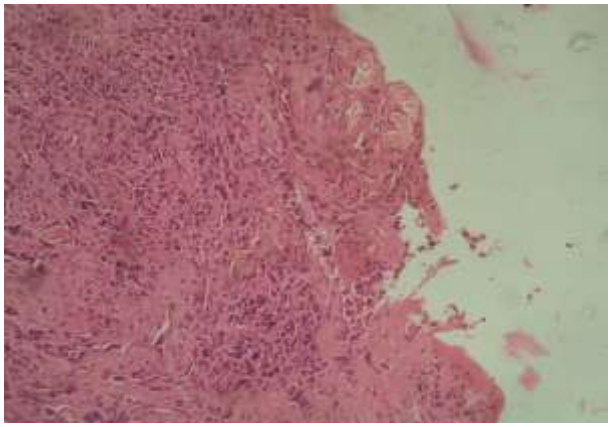

Fig-2: ALM with telangiectasia and fibrosis; x200 H&E.

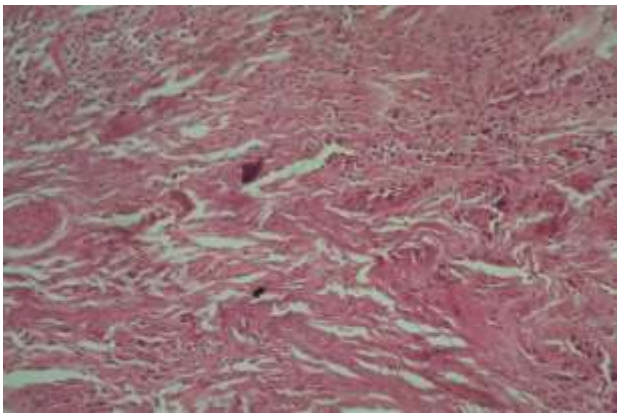

Fig-3: ALM, fibrosis; x200 H&E

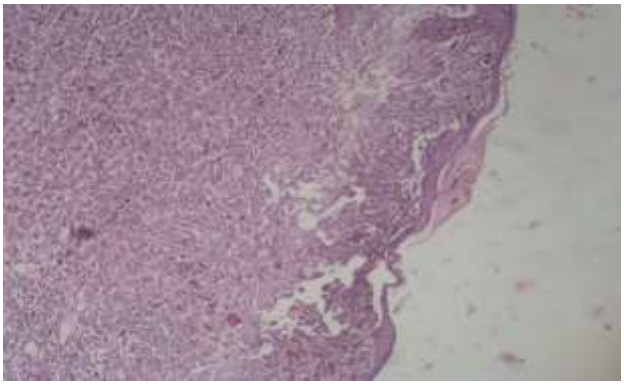

Fig-4: Nodular melanoma with thinning of the overlying epidermis; x100 H&E.

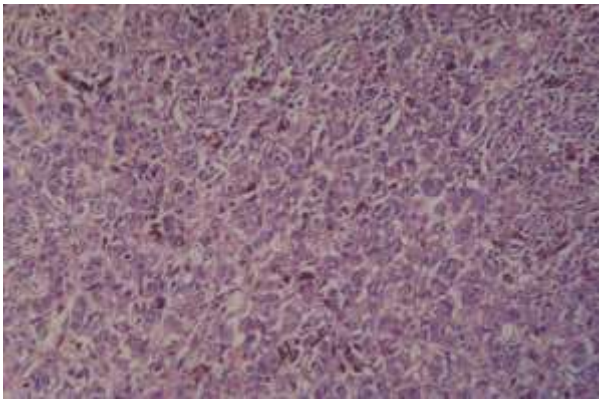

Fig-5: Nodular melanoma, sheets and nests of pleomorphic cells with melanin pigment; x200 H&E

Maximum number of cases of extracutaneous melanoma showed mitosis, necrosis and spindle morphology (Table 2) (Figures.6,7,8,9,10).

Table 2: Histopathological features of extracutaneous malignant melanoma

Aspect	Extracutaneous malignant melanoma (n=4)
Tumor infiltrating lymphocytes	
Brisk	2/4
Non brisk	2/4
Absent-	
Tumor thickness(in mm)	18.00 + 9.09 (mean)
Necrosis	2/4
Mitosis	
<5/10 HPF	4/4
>5/10 HPF	0/4
External pigmentation	3/4
Desmoplasia	1/4
Cell Type	
Spindle	2/4
Epithelioid	1/4
Mixed	1/4

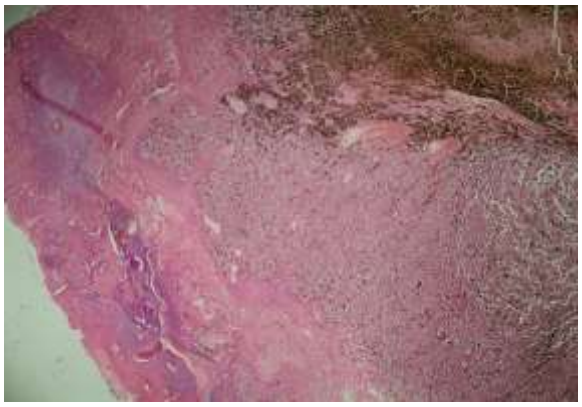

Fig-6: Conjunctival malignant melanoma showing surface ulceration; x40 H&E.

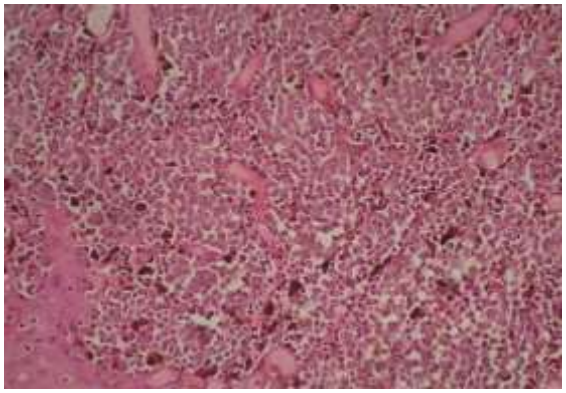

Fig-7: Conjunctival melanoma with melanin pigmentation and epithelioid morphology of the tumor cells; x200 H&E.

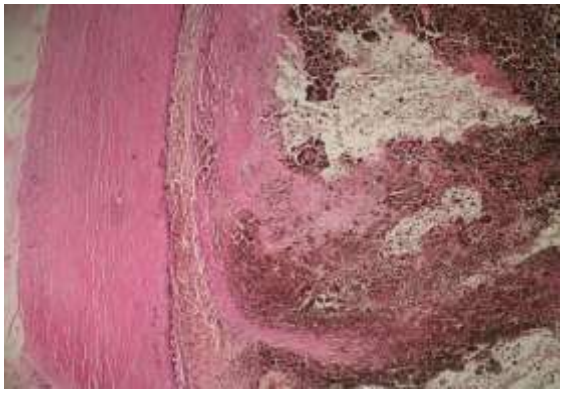

Fig-8: Choroidal melanoma; x40 H&E

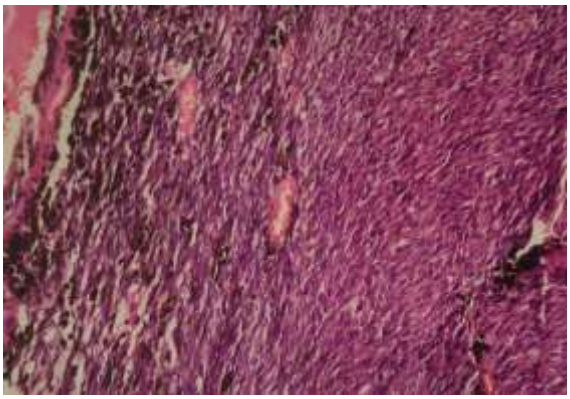

Fig-9: Malignant melanoma, choroid showing spindled morphology of tumor cells; x200 H&E

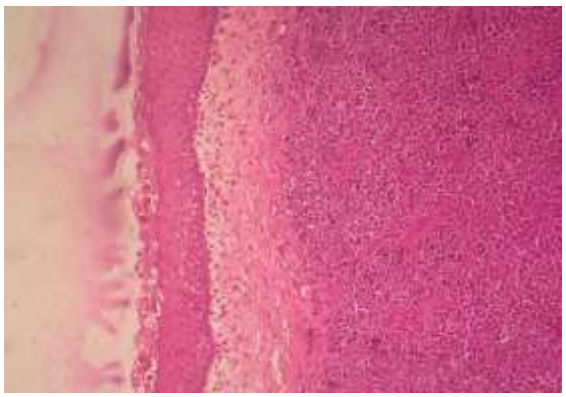

Fig-10: Malignant melanoma, nasal cavity underlying an epithelium that has undergone squamous metaplasia; x40 H&E

Out of the 38 cases of melanocytic nevi, 37 were benign nevi and the largest number of cases{20 (52.6%)} were of intradermal type (Figures.11,12). There was one case each of dysplastic nevus and lentiginous melanocytic nevus (Figures.13,14). All the extracutaneous cases {8(21.1%)} were conjunctival and six of these were of the subepithelial type and two were of compound type (Figures.15,16) (Table 3). Histopathological features of cutaneous malignant melanoma.

Table 3: Histopathological features of cutaneous malignant melanoma

Aspect	**Cutaneous malignant melanoma (n=8)**
Tumor infiltrating lymphocyte	
Brisk	2/8
Non-Brisk	5/8
Absent	1/8
Growth Phase	
VGP	8/8
RGP	2/8
Junctional Activity	5/8
Pagetoid spread	6/8
Clark Level	
I	0/8
II	0/8
III	0/8
IV	5/8
V	3/8
Breslow thickness	17.19 + 13.22 (mean)
Necrosis	4/8
Mitosis	
<5/10 HPF	2/8
>5/10HPF	6/8
Pigmentation	5/8
Desmoplasia	3/8
Cell Type	
Epithelioid	4/8
Spindle	0/8
Mixed	4/8

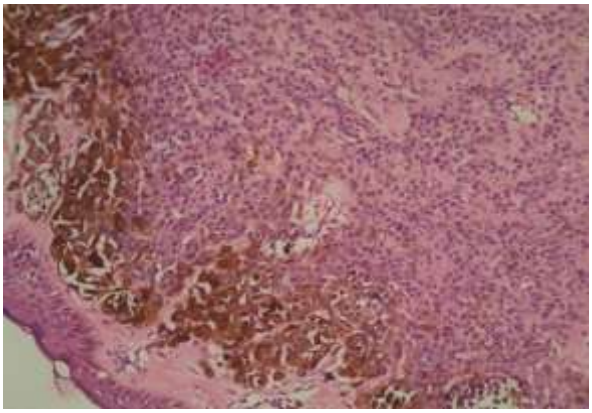

Fig-11: Intradermal melanocytic nevus, showing type 'A' or epithelioid cells and type 'B' cells (lymphocyte like); x200 H&E

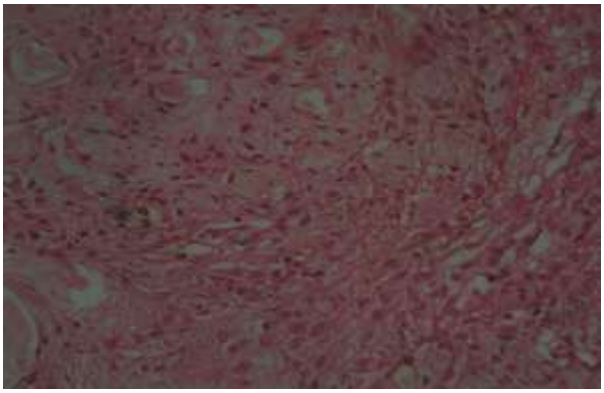

Fig-12: Intradermal melanocytic nevus showing type "C" cells (spindle cells) and neurotization as well; x400 H&E

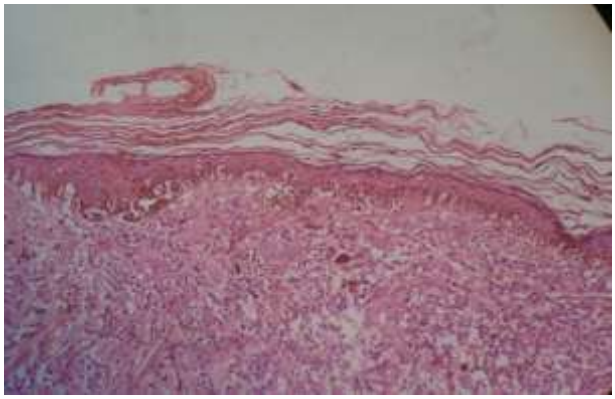

Fig-13: Dysplastic nevus with brisk tumor infiltrating lymphocytes; x100 H&E.

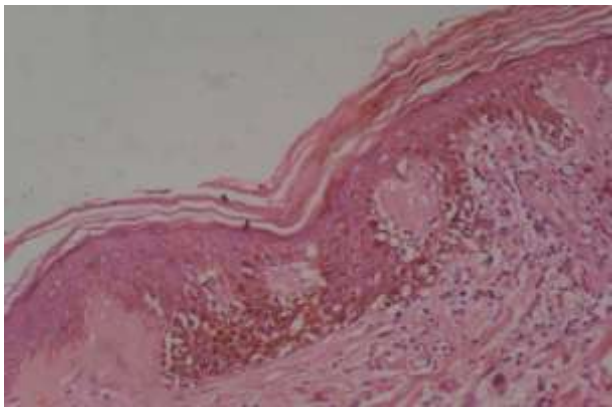

Fig-14: Dysplastic nevus showing bridging of nests between rete ridges; x200 H&E.

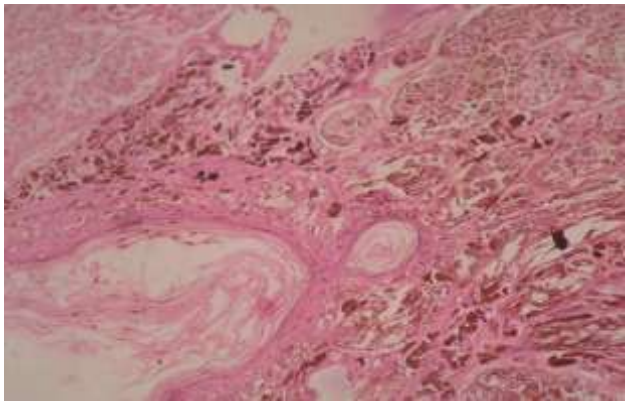

Fig-15: Compound type melanocytic nevus showing junctional activity as well as an intraepidermal nest; x200 H&E

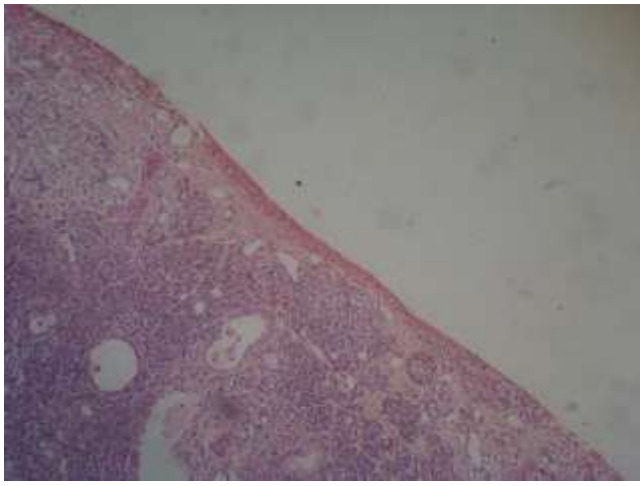

Fig-16: Subepithelial conjunctival nevus; x100 H&E

Dysplastic nevus was seen in a 33 years male, on the thigh measuring 2 mm with pigmentation that was progressively increasing and was histologically junctional in type. The lentiginous melanocytic nevus was seen in a 24 years female in the right infraclavicular region, measuring 5 mm in size with pigmentation, clinically diagnosed as a Spitz nevus with a mixed spindle and epithelioid cell type. There were no mitotic figures, no lamellar or concentric eosinophilic fibroplasia, or adnexal involvement. There was no dysplasia, senescence, neurotization and no tumor infiltrating lymphocytes and a normal epidermis (Table 4).

Table 4: Characteristics of melanocytic nevi

Aspect	Benign nevi	Dysplastic nevi
Component		
Compound	8/36	0/1
Dermal/Subepithelial	28/36	
Junctional Activity	6/36	1/1
Mitosis		
<5/10 HPF	0/36	1/1
>5/10 HPF	0/36	
Pigmentation-	36/36	1/1
Lamellar fibrosis	0/36	1/1
Concentric eosinophilic fibrosis	0/36	0/1
Dysplasia	0/36	1/1
Senescence	34/36	0/1
Neurotization	19/36	0/1
Adnexal Involvement	0/36	0/1
Tumor infiltrating lymphocytes		
Brisk		1/1
Non Brisk	16/36	
Absent	20/36	
Cell type		
Epithelioid	11/36	1/1
Spindle	20/36	
Mixed	5/36	
Epidermis		
Atrophic	5/36	1/1
Normal	11/36	0/1
Normal and Atrophic	20/36	0/1

DISCUSSION

Few if any studies have been done on melanocytic neoplasms and melanoma in the Nepalese population. However, with the rising incidence of melanoma worldwide, a study on the clinicopathological features of these neoplasms was much needed. This study was conducted to define the same

Age and sex distribution

The mean age at presentation for melanocytic neoplasms as a whole was 37+ 18 yrs and the mean age for melanoma was 50 + 17 yrs, however the youngest patient in this group was a 20 years old male who had xeroderma pigmentosum.Kraemer *et al* [4] also reported a median age of onset of 19 yrs on reviewing 297 articles with 830 XP patients from a survey of the medical literature from 1874 to 1982. The age of onset is similar to the case of XP seen in our study.Hussein *et al* [3], examined 43 cases of cutaneous melanocytic neoplasms in which 12 were benign nevi (BN), 10 dysplastic nevi (DN), and 21 cutaneous melanomas (CMs). The DN and CMs were more common in men than in women (2: 1 and 1.5: 1, respectively) while BN were more common in women (2 : 1). The average age incidence was 33± 5, 38± 7 and 54± 3 years, for BN, DN and CM, respectively.

Melanoma is more common in men than in women and usually affects elderly people. In a study conducted by Borbola K et al, there were 70 young (under 30 years) patients who were treated for malignant melanoma. The incidence of melanoma under the age of 30 was 3.3%. In young adulthood the main risk factors were the number of atypical nevi and repeated or severe sunburns in childhood. The skin type was also an important risk factor. 50% of the melanomas in young women developed on the trunk. Authors could not prove any relationship among hormonal factors, pregnancy and the development of the melanoma [5]. At present, men have a one in 58, and women a one in 82 chance of developing CM in their lifetime, worldwide [6]. The male sex predilection of CM may be because it is possible that male population carries some BRAF gene alterations [7]. BRAF contains several sites of natural variation. Some variants are more likely to be found in people with CM than in those that do not have CM. The variants can only confer a higher risk of having CM in men who carry them [7]. Melanoma was seen as frequently in men as in women in Nepal, this may in one way reflect that women folk in Nepal are probably just as involved in outdoor activities as men whereas melanocytic nevi was more commonly seen in women , this could be due to the fact that women are more conscious of their skin.Moreover, all CM cases were of vertical growth phase and occurred frequently in elderly people. It is possible that elderly individuals have more difficulty in recognizing changes in their skin as well as in visiting their physicians. Therefore, diagnosis of skin cancer is delayed.

Site of melanocytic neoplasms

The site of involvement in cases of melanocytic nevi were most common in the head and neck region (25/38), which is similar to the study conducted by Hussein et al where the most number of benign (7/12) and dysplastic nevi (8/10) occurred in the head and neck region as well [3]. Azam *et al*, also had similar results [8]. Our study shows that malignant melanoma was most commonly seen in the extremities, which is similar to the study conducted by Cochran A J [9], where the most common site of presentation were the extremities (lower limb) and head and neck region as well. Four cases were extracutaneous in which one each was seen in the conjunctiva and nasal cavity and two were seen in the choroid. The greatest incidence of CMs on the lower extremities (volar aspect of the foot) is in contrast to its topographical distribution in Caucasians, face and neck being the most common sites in them [10]. This finding could be due to the instability of melanocytes on the plantar side of the skin and though the foot has the highest density of melanocytes per unit area, following the face, this high density cannot compensate for its increased exposure to UV radiation [3].

Clinicopathological concordance in the diagnosis of melanocytic neoplasm

Out the total 50 cases of melanocytic neoplasm, clinicopathological concordance was seen in 60% (30/50) and discordance in 40% (20/50). Breitbart EW *et al*, have stated that the clinical diagnosis of melanoma is based on the subjective evaluation of objective measurable parameters (criteria). The accuracy of melanoma diagnosis by dermatologists is only 75%. Particularly difficult is the diagnosis of precursors or early stages of MM [11]. This is consistent with our study where out of 12 cases nine (75%) were correctly clinically diagnosed as melanoma.

Size

The median size of melanocytic nevi and malignant melanoma was 7.50 mm and 15 mm respectively in our study, which can be supported by Leung KM et al's findings, where Caucasian patients tended to present with smaller lesions(average 4.4 mm,±1.964) compared with Asian patients (average 5.3 mm, ±3.64, $p<0.001$) [12].

Histopathological characteristics

Melanocytic nevi

The largest number of cases in our study among melanocytic nevi were of cutaneous intradermal type (20/36).Hussein et al found the same, intradermal cutaneous nevi being (7/12)the commonest type and most dysplastic nevi of the compound type [3]. Azam S *et al* also had similar findings in their study [154/18]. In our study most conjunctival nevi were of subepithelial type which is in contrast to Alkatan HM *et al* findings where most conjunctival nevi were of compound type72% (n=76) [13]. In our study, in melanocytic nevi, cell type was predominantly spindle in benign nevi, and was epithelioid in dysplastic nevus. Pigmentation was seen in all the melanocytic nevi. In contrast in Hussein *et al's* study, cell type was predominantly epithelioid in both benign and dysplastic nevi. Pigmentation was seen in all cases in their study too [3]. In our study, senescence and neurotization was

seen in 34 and 19 cases out of the 36 cases of benign nevi respectively. Hussein et al had similar findings [3].

Extracutaneous melanoma

Among the four cases of extracutaneous melanoma, three were ocular and one was seen in the nasal cavity. In another study conducted by Hussein MR [14], the author presents a large series of extracutaneous malignant melanomas that he came across through his 15 years of histopathology practice, the case series includes ocular (24 cases), metastatic (11, 3, and 1 case in lymph node, bone, and liver, respectively), sinonasal (five cases), anorectal (two cases), esophageal, and orbital (one case each) malignant melanomas. Though our study sample is relatively small, it nevertheless points towards the trend of extracutaneous melanoma more commonly occurring in the ocular region which is similar to Hussein MR's study [14]. The high median tumor thickness of 16 mm could be due to late symptomatic presentation of these tumors, as in most of their sites of occurrence, the tumor growth was less likely to be visible to the patient.

Cutaneous melanoma

Out of the eight cases of cutaneous melanoma, largest number of cases were of nodular type (6/8), followed by acral lentiginous type, (2/8), both of which presented in VGP. One of the acral lentiginous melanoma also showed features of regression. This is similar to the study conducted by Hussein *et al* [3] in which most of the lesions was nodular melanomas (19 cases). The remaining two cases were superficial spreading melanomas. However, Mukhopadhyay S *et al* [15] found that out of 11 cases of cutaneous melanoma, six (54.54%) were of superficial spreading variety and only one (9.1%) of nodular variety. The greater incidence of nodular melanoma in our series reflects an aggressive biology and possibly also as a result of lack of awareness in patients and subsequently late presentation. In our study, tumor infiltrating lymphocytes were non brisk in the largest number of cases (5/8), followed by brisk in two cases, which was similar to Hussein *et al's* observation [3], again reflecting a poorer prognosis and a possibly worse outcome. In our study, growth phase was vertical in all the cases (8/8),junctional activity was seen in five out of eight cases. Pagetoid spread was seen in six out of eight cases. This is similar to the study conducted by Hussein et al in which growth phase was vertical in all cases (21/21), junctional activity was present in six out of 21, pagetoid spread in four out of 21 [3]. In our study, Clark's level of invasion was IV in the largest number of cases (5/8), followed by V (3/8). Median Breslow thickness was 14 mm; necrosis was seen in four out of eight cases. This was most likely the result of late presentation. Hussein *et al* similarly found a Clark's level of invasion V in most number of cases (10/21), followed by IV (6/21). Breslow thickness was 6 + 0.5 mm. Necrosis was seen in 12 out of 21 [3]. In our study, mitosis was >5/10HPF in the largest number of cases (6/8) which again denotes a worse prognosis. In the study conducted by Cochran AJ [9], 142 tumors were examined for mitotic figures. Seventy six (53%) showed less than one mitosis per high-power field and 66 (47 %) showed more than one mitosis per high-power field. The 5-yr survival rate of low mitotic rate tumors was significantly better ($P<0.02$) and the incidence of nodal metastasis in this group was significantly less ($P<0.05$), but no other significant differences in behavior were noted [9]. In the same study, ulceration was present in 76 (46 %). In these cases the 5-yr survival rate was significantly lower ($P<0.05$), dissemination occurred significantly more frequently ($P<0.05$) and local recurrences were significantly less frequent ($P<0.00l$) [9]. This is similar to our case in which ulceration was seen in five out of 12 cases (41.7%). However as the patients were lost to follow up, the instances of recurrences, metastasis or survival rates of the patients could not be recorded.

The clinicopathologic features of melanoma in Nepal reflect an aggressive biology. In our series, several clinicopathological features suggest an aggressive behavior for malignant melanomas including:

(1) high age incidence (people older than 54 years have more aggressive tumors);

(2) the large width and great depth of these lesions (neoplasms >1.5mm in depth have a worsened prognosis [16].

(3) the high mitotic counts;

(4) ulceration of the lesions (ulcerated tumors are more aggressive than nonulcerated ones);

(5) the nodular type of melanoma (nodular melanomas have worse prognosis);

(6) the epithelioid cytology of the tumors [17,18].

Melanocytic neoplasms in Nepal

Our hospital is one of the major referral centers in Nepal. There is thus a fair inflow of patients and we get a variety of histopathology specimens in our department. Thus we were able to undertake this study, with a total of 50 cases of melanocytic neoplasms. Melanoma is a rare neoplasm in Nepal and its etiology seems to be related to sun exposure. The small sample size in our series reflects the rare incidence of this tumor in Nepal. Melanoma was most frequent in the extremities in our series which is a sun exposed area of the body, which suggests UV as a possible contributor to melanomagenesis. Nevertheless, compared with Western societies, malignant melanoma is rare in Nepal [19] probably due to a lack of genetic predisposition among Nepalese. This could be due to the high mean age at diagnosis (50±17 years), as hereditary melanoma usually occurs in the third decade of life. Majority of the patients presented with single rather than multiple lesions whereas most hereditary melanomas present as multiple tumors. It is also possible that rarity of melanoma in the Nepalese is due to the wheatish skin of the Nepalese allowing less penetration to UV rays. In

support of this theory it has been found that split preparations of the stratum corneum and epidermis from fair and black skin (relatively impenetrable) can transmit 29 and 7% of UVB, respectively [20, 21]. Krishnamurthy S found that geographic patterns of melanoma in Indians are similar with those in white Caucasians. Thus ultraviolet light exposure may also be involved in its etiology in non-white Caucasians, such as Indians [22].

This study points out that melanocytic nevi is quite common in Nepal and it seems to involve the female population more frequently, whereas, malignant melanoma is a rare disease in Nepal that affects both men and women and is likely to represent a sporadic rather than familial lesion. Also, it has different topographical distribution than that in Western societies. The striking difference from Western series is the incidence of nodular melanoma ; in the West this represents 15–30% of melanomas, with superficial spreading being the majority [3]. In our study the incidence of nodular melanomas among the CM was higher. This probably could be due to late presentation in our context due to lack of awareness in our people on its fatal nature.

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