ORIGINAL ARTICLE

MORPHOLOGICAL SPECTRUM OF NON MELANOMA SKIN CANCER EXPERIENCE AT A TERTIARY CARE HOSPITAL IN KARACHI, PAKISTAN

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ABSTRACT

Background: Jinnah post graduate medical center is a major tertiary care hospital in Karachi. People of varying skin color from different ethnic groups in this cosmopolitan city present to this hospital. The current study was designed to determine the histopathological spectrum of non melanoma skin cancer including basal cell carcinoma and squamous cell carcinoma in skin biopsy cases reported at pathology department, basic medical sciences institute, JPMC.

Methods: This retrospective cross sectional study included 142 cases of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) diagnosed over5-year duration at department of pathology, Basic Medical Sciences Institute, Jinnah Post Graduate Medical Center, Karachi. World Health Organization histologic classification of keratinocytic skin tumors was followed for subtyping of BCC and SCC.

Results: Out of the total of 142 NMSC cases, 86 (60%) were (BCC) and 56 (40%) were (SCC). Majority among SCC i.e. 33 (58.9%) were well differentiated carcinoma. The most common single morphology in BCC was the nodular variant constituting 56 (65.1%) cases. Mixed composition of BCC constituted 25 (29%) cases. A combination of two histological patterns was observed in 22 (25.5%) cases while 3 (3.5%) cases showed more than two morphologies.

Conclusion: Well differentiated squamous cell carcinoma was the most common variant of cutaneous SCC. Nodular variant was the most frequently observed subtype amongst BCC. A significant number of BCC cases revealed mixed histopathological patterns, a novel finding of the study. Our data include people from different ethnicities with variable skin color and thus provides useful reference for future studies.

KEYWORDS: Carcinoma, Basal Cell, Squamous Cell, Skin cancer.

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INTRODUCTION

Non melanoma skin cancer (NMSC) is comprised of two cutaneous malignancies, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSC is the most common malignancy in some countries with Caucasian population. Although it is less common in people of color, a greater morbidity and mortality has been reported in this group. Early detection can decrease morbidity and expense of treatment. Basal cell carcinoma is more prevalent in Caucasians while squamous cell carcinoma in dark skinned population. However, the Asians and Hispanics possess intermediate pigmentation skin and thus share features of both Caucasians and dark skinned population.[1]

Non melanoma skin cancer (NMSC) is the most frequent malignancy in United States. Basal cell carcinoma (BCC) accounts for 80% while squamous cell carcinoma (SCC) accounts for 20% of NMSC cases in United States. A 50-200% rise in incidence has been reported in a 30- year based cancer registry.[2]Significant disease burden due to NMSC has been reported in Australia. The annual cost of diagnosis and treatment of this malignancy in 2010 was calculated to be A$511 million.[3]According to Karachi Cancer Registry published in 2004, skin cancer constituted 2.6% of all cancers.[4]

Sunlight exposure is associated with development of NMSC. The role of ultraviolet radiation in carcinogenesis of BCC and SCC has been reported by multiple studies in literature. Light coloring of skin, hair and eyes, inability to tan and skin disorders such as actinic keratosis are some of the leading causes. Other risk factors include male gender, skin ulcers, chronic scarring, burns, ionizing radiations and arsenic ingestion. Immunocompromised patients and organ transplant recipients are at a high risk of acquiring NMSC and more commonly squamous cell carcinoma. The clinical behavior of BCC and SCC depends greatly upon its morphological subtype. [5, 6]The current study was designed to determine the histopathological spectrum of NMSC and its association with gender and mean age in skin biopsy cases reported at a major tertiary care public sector hospital of Karachi.

METHODS

This retrospective cross sectional study included diagnosed cases of BCC and SCC retrieved from the archives of department of Pathology, Basic Medical Sciences Institute, JPMC, over a 5-year period from 01-01-2012 to 31-12-2016. Ethical review board of BMSI approved the research project. A total of 142 NMSC cases were subjected to histopathological review. Formalin fixed, paraffin embedded blocks, Hematoxylin & Eosin stained slides and surgical pathology records were used. All the slides were studied under light microscopy using scanner (4x), low power (10x), and high power (40x) lenses. Tumors were analyzed considering histological type, age and gender of the patient. World Health Organization histologic classification of keratinocytic skin tumors was followed for the subtyping of BCC and SCC.7Melanoma and metastatic tumors were excluded from the study. SPSS version 22.0 was used for data analysis. Clinical characteristics were summarized in terms of frequencies and percentages. Association between histological pattern, patients' age and gender was analyzed using Fisher Exact test. The findings were considered statistically significant at $p<0.05$.

RESULTS

Out of the total of 142 NMSC cases, 86 (60%) were basal cell carcinoma (BCC) and 56 (40%) were squamous cell carcinoma (SCC). The age range was between 15-90 years. The overall mean age came out to be 56.68± 15.01 years. Majority of BCC cases i.e. 26 (30.2%) presented in seventh decade of life and most of SCC cases presented in sixth decade i.e. 23 (41%). The distribution of NMSC according to age groups as shown in Table 1. Slight male preponderance was noticed with an M: F ratio of 1.3:1. Certain BCC cases with single and mixed patterns however, showed female predominance (Table 2).

Table 1: Shows the Distribution of Non Melanoma Skin Cancer According To Age (n=142)

Age group	<30	31-40	41-50	51-60	61-70	>70	Total	Mean age
BCC	09 (10.46%)	04 (4.6%)	15 (17.4%)	22 (25.5%)	26 (30.2%)	10 (11.6%)	86	57.2
SCC	03 (5.3%)	05 (8.9%)	11 (19.6%)	23 (41%)	06 (10.7%)	08 (14.2%)	56	55.8

Table 2: Shows the Distribution of Squamous Cell Carcinoma According to Morphological Type, Gender and Mean Age (SCC, n=56)

SCC Morphological type	No. of cases	Percentage	M/F	Mean Age	P value
Well differentiated	33	58.9%	18/15	56.33	0.000**‡
Moderately differentiated	20	35.7%	13/7	53.80	
Poorly differentiated	03	5.4%	2/1	65.00	
Total SCC cases	56	100%	33/23	55.89	

Grading of squamous cell carcinoma was established according to morphology in well differentiated, moderately differentiated (Figure 1) and poorly differentiated groups. Table 3 describes the division of all 56 cases of squamous cell carcinoma according to morphological grade, gender and mean age (p=0.000)

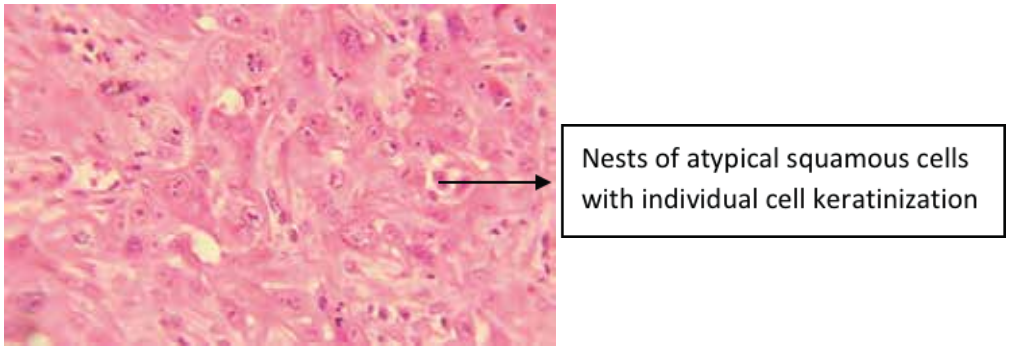

Figure 1: Photomicroraph SP.NO. 15-4953 A1.H&E 40X. Moderately differentiated squamous cell carcinoma with individual cell kertainization.

The most common single morphology in BCC was the nodular variant constituting 56 (65.1%) cases. A considerable number of BCC cases 25 (29%) showed mixed compositions. A combination of two histological patterns was observed in 22 (25.5%) cases while 3 (3.5%) cases showed more than two morphologies. Among mixed histological patterns, the nodular component was predominantly identified in combination with other morphologies (Figure 2). More than two BCC morphologies included various combinations of nodular, solid, pigmented, morphoeiform and adenoid patterns (Table 3). Association between histological subtypes, gender and mean age was statistically significant (p=0.000)

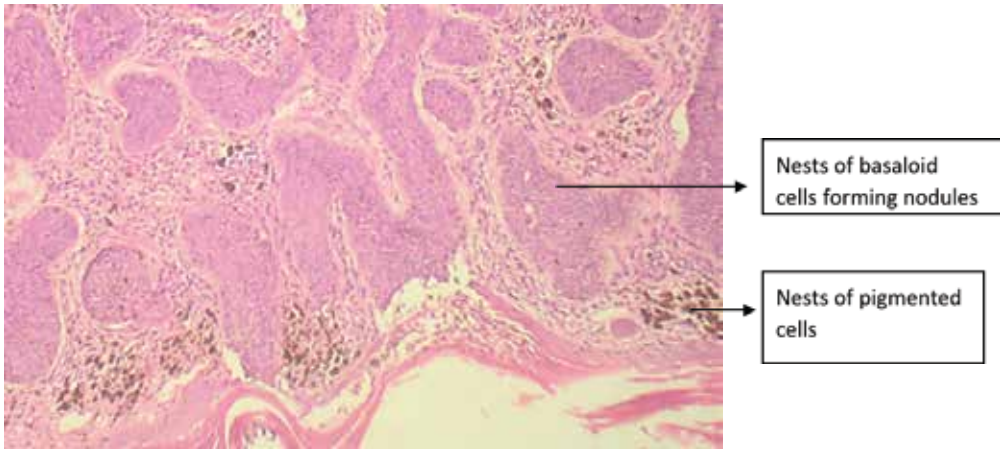

Figure 2: The figure shows the Photomicrograph SP.NO: 14-4420. H&E. 10X. Basal cell carcinoma with nodular and pigmented patterns.

Table 3: Shows the Distribution of Basal Cell Carcinoma According to Morphological Type, Gender and Mean Age (BCC, n=86). **p-value<0.0001,ǂFisher-exact test)

BCC variants with single morphology	No. of cases	Percentage	M/F	Mean Age	P value
Nodular	56	65.1%	25/31	60.30	
Pigmented	02	2.3%	1/1	71.50	
Adenoid	01	1.2%	1/0	62.00	
Solid	01	1.2%	0/1	50.00	**0.000**ǂ**
Basosquamous	01	1.2%	1/0	28.00	
Superficial	0	0%	-	-	
Morphoei form	0	0%	-	-	
BCC Mixed histological patterns	**No. of cases**	**Percentage**	**M/F**	**Mean Age**	**P value**
Nodular & Pigmented	07	8.1%	5/2	37.14	
Nodular & Solid	05	5.8%	3/2	65.00	**0.000**ǂ**
Nodular & Adenoid	02	2.3%	0/2	37.50	
Nodular & Morphoeiform	02	2.3%	2/0	65.50	
Solid & Adenoid	02	2.3%	1/1	60.00	
BCC with focal squamous pattern	04	4.6%	4/0	48.00	
BCC with more than two morphological patterns	03	3.5%	3/0	52.00	
Total BCC cases	**86**	**100%**	**46/40**	**57.20**	

DISCUSSION

Non melanoma skin cancer is a fairly common malignancy in South Asian region. Knowledge of morphological subtypes of both BCC and SCC is significant in developing an approach towards their accurate treatment. To our knowledge no extensive study regarding the histopathological subclassification of NMSC is available in the literature from this region. The diagnosed cases of NMSC reported during the review period were 142 constituting 6.1% of all the malignancies reported at the department of Pathology, BMSI. This figure demonstrates a significant disease burden in the community. Literature search revealed variable results from different regions of Pakistan regarding skin cancer prevalence. A frequency of 7.2% was reported by a study at AFIP Rawalpindi.[8]An increased trend was noted in a Peshawar based study, performed on Pakistani natives and Afghan refugees where the frequency of skin cancer was 8.9% and 13.3% respectively. This difference in results may be attributed to a higher altitude in the northern KPK province and fair complexion of the people.[9]A frequency of 2.2% was reported in the five-year annual cancer registry of Shaukat Khanum Cancer Hospital and Research Center between 2010 and 2014. This finding may be because SKMCH reported skin cancer frequency from all over Pakistan.[10]

The current study showed BCC predominance with 60% cases in comparison to 40% cases of SCC. Similar statistics were described by Ikram et al., with 58% BCC and 42% SCC cases respectively. Soomro et al. in Larkana, Sindh observed 65.5% BCC and 34.4% SCC cases. Shaukat Khanum Cancer Hospital and Research Center annual registry of 2010 also reported a predominance of BCC with 54.6% cases in comparison with 45% of SCC cases. Another study from JPMC showed 48% BCC against 40% SCC cases.[10, 11, 12, 13] However, a different data was reported by a Lahore based study which showed more

SCC cases (80%) and less BCC cases (20%). Furthermore Baruah et al. from Sikkim India noted 64% SCC and 36% BCC cases. Similarly the data from Manipur India by Laishram et al. showed a predominance of SCC (57%) in comparison to 43% BCC cases.[14,15,16] These differences highlight the significance of geographical location, skin color and exposure to risk factors. The above statistics representing majority of population from both Indian and Pakistan side of Punjab reveals a higher frequency of SCC. This may be related to field workers and farmers who are exposed to sunlight for longer duration. Since JPMC is a tertiary care unit of Karachi where patients from different ethnicities including Afghani and Bangladeshi origin are treated, our set of data carries a significant representation of all ethnicities and skin color from this cosmopolitan city.

Gender distribution in the current study revealed a male predominance in NMSC cases with an M: F ratio of 1.3:1. This finding is consistent with the study by Asif et al. in which the ratio was 1.2:1. A male to female ratio of 1.85:1 was reported by Soomro et al. An Indian study documented 1:0.96 of M:F ratio.[8,12,16] This male predominance endorses the fact that males in our part of the world are more often involved in outdoor activities rendering them prone to prolonged sunlight exposure whereas women are mostly confined to their homes. Also the prevailing religious and cultural traditions of hijab to cover the head and face reduce UV light exposure to females in general.

The age range of NMSC in the current study was quite wide, ranging from 16-90 years. This corresponds to 17-90 year documented by Laishram et al. and 10-85 year reported by Aandani and Ganatra. Mean age for BCC as noted in the present study was 57.2 year which is in accordance with the mean age of 59.4 year by Ahmed et al. and 55 year described by Bukhari et al. Furthermore, in the present study mean age observed among SCC cases was 55.8 year which is close to the mean of 58 year recorded by Ahmed et al. Bukhari et al. also reported a slightly different mean of 50.2 year. However higher means of 62.5 year and 62.1 year were observed in Iranian population by Beheshtiroy and Hajmanoochehri and Ochicha et al., respectively. This variation may be attributed to large sample size of the studies, a different geographical location and late presentation of the patients.[14, 16, 17, 18, 19, 20]

The present study highlighted that majority i.e. 30.2% of BCC patients were in seventh decade followed by 25.5% in sixth decade. Laishram et al. and Baruah et al. also reported majority of cases in this age group. Furthermore Kumar et al. documented that patients between 60-80 year age group were the most affected. Amongst SCC 41% cases belonged to patients in the sixth decade of their lives, a finding that is supported by Ochichaet al. with 40% cases in the same age group. Moreover, Behishtiroy and Hajmanoochehri also recorded most of SCC cases in the sixties. The increased frequency of NMSC with rising age reflects prolonged UV light exposure and lack of DNA repair. [15, 16, 19, 20, 21]

In the present study a considerable number of cases i.e. 10.4% presented in less than 30-year age group. Amongst which 2.3% were in the teenage group while 8.1% were in their twenties. Ahmed et al. described 3.4% and Asif et al. reported 1.3% BCC in the third decade. Similarly, 5.3% of SCC cases were found in the third decade in the current series. Ahmed et al. showed 1.7% SCC cases under 30 year age group. The discordance may be due to larger sample size and longer study duration by Ahmed et al. NMSC in younger patients relate to the possible association of genetic syndromes such as basal cell nevus syndrome, Xeroderma pigmentosum and albinism with the risk of early development of NMSC in younger population.[8, 18] It is important to diagnose both BCC and SCC at an early age because some of them are genetically predetermined and could provide a link to an inherited disorder.

In the current study, the most common histological grade of SCC was well differentiated representing 33 (58.9%) followed by 20 (35.7%) of moderately differentiated (Figure 1) and 3 (5.4%) poorly differentiated SCC cases. This finding is parallel to a study by Kubo et al. which demonstrated 60.8% well differentiated, 26% moderately differentiated and 13% poorly differentiated tumors. Laishram et al. support this finding by reporting the frequencies as 65%, 22.5% and 12.5% for well, moderately and poorly differentiated cases respectively. Baruah et al. also reported majority i.e. 66.7% of well differentiated SCC. The higher number of poorly differentiated tumors in these studies may be due to difference in sample size and late presentation of the patients. The early detection of NMSC can help in accurate management and complete cure of the disease. Furthermore, Christenson et al. described a slightly different data with 84% well differentiated tumors and 9% and 6% moderately and poorly differentiated tumors respectively. Their result possibly reflects the selection of younger than 40 years of patients in their series. [1, 15, 16, 22, 23]

Various single and mixed morphological variants of BCC were recorded in the current series. The nodular subtype represented the most common single morphological pattern with 56 (65.1%) cases. Similarly, Kumar et al. and Hussain et al. reported nodular BCC as the most frequent subtype i.e.77.8% and 56.6% respectively. Furthermore, Laishram et al. also observed nodular variant as the most frequent single pattern. In the present study 2(2.3%) pigmented BCC cases were recorded. Hussain et al. showed 6.6% whereas Kumar et al. revealed a higher frequency of 22.2%. Moreover, in our series BCC cases had generalized body distribution in comparison to Hussain et al. which selected only eyelid

cases. This finding demonstrates importance of the involved site. The possible reason of a higher number of pigmented subtypes of BCC by Kumar et al. may be a genetic predilection for pigmented lesions in the Indian population.

Adenoid and basosquamous variants of BCC represented 1(1.2%) cases each in the current study. Hussain et al. described 6.6% of adenoid and 13.3%of basosquamous variants. This discordance may be due to a smaller sample size and inclusion of only eyelid cases in their series. We did not come across superficial or morphoeiform variants as sole entities may be due to the late presentation of patients as cited by other studies. Superficial BCC is an early form and sometimes undergoes spontaneous regression. Biopsy at a late stage may not be helpful in diagnosis of this entity. Morphoeiform BCC is a notorious variant which has been reported to have an aggressive clinical behavior with a potential of extensive tissue destruction. Thus, early diagnosis and subtyping of BCC may help clinicians for a good treatment approach. [6, 16, 17, 21, 24]

Mixed morphological patterns (Figure 2) constituted 25(29%) BCC cases in this study which is comparable to 38.5% by one of the studies.[25]Nodular subtype constituted a predominant pattern found in combinations with other histological subtypes. BCC with more than two morphological forms constituted 3(3.5%) of all lesions. Extensive literature search did not reveal studies with similar details related to mixed patterns of BCC. The present study is a novel effort in studying the mixed morphological subtypes of BCC in population with variable skin color presenting at JPMC. The results of the current study will provide a baseline data on non melanoma skin cancer and their histopathological subtypes in this region. It will be a useful reference for advance level researches and genetic studies related to skin cancer. It is recommended that cancer registry should be maintained to record the accurate frequency of the disease. Since NMSC is a preventable disease, public awareness programs highlighting the risk factors, especially related to Ultraviolet rays of sunlight and use of sun screens should be promoted. Steps towards early diagnosis and treatment should also be encouraged.

CONCLUSION

NMSC constitutes a significant disease burden (6.1%) in our setup. Well differentiated squamous cell carcinoma was the most common variant of cutaneous SCC. Similarly, Nodular variant was the most frequently observed subtype amongst BCC cases. Mixed patterns BCC comprising of combinations of various morphological arrangements, were observed in a significant number of cases. We did not come across superficial or morpheaform variants as individual entity. The current study included varied ethnicities with different skin color presenting to JPMC and thus provides significant data from this region.

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