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Original Research Article

Histologic pattern analysis of cutaneous basal cell carcinoma at a tertiary care hospital in South India

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ABSTRACT

Background & Objectives: Basal cell carcinoma (BCC) is one of the common malignant disease of the skin worldwide. An attempt at a simplified, accurate histologic classification of BCC based on histologic growth patterns is done in this study. This paved way to the concept of risk typing BCC into low and high-risk types.

Materials and Methods: This is a retrospective descriptive study of skin biopsies diagnosed as BCC between 2010 and 2018 in the Department of Pathology in a tertiary care teaching hospital in Karnataka. H&E stained sections were reviewed, histopathologically subtyped and further categorized into high and low risk types. IHC for BerEP4 was done in ten diagnostically challenging cases. The patients were followed up for six months after the study period.

Results: 79 cases of BCC were studied with majority of them being classified as high risk BCC (83.54%), with nodular type (51.89%) being the most common histological subtype. BCCs were seen predominantly in patients in the sixth decade with a female preponderance in both high and low risk BCCs. Majority of the patients with genetic predispositions were of young age and included xeroderma pigmentosa and oculocutaneous albinism. IHC for BerEP4 showed strong and diffuse membranous staining in all ten cases. Recurrence was noted in two cases and metastasis following three recurrences was noted in one case.

Conclusion: An accurate histologic classification of BCC based on growth pattern is of great significance as it reflects the biological behaviour of the tumour. Risk typing BCC into high and low risk types further guides the management of BCC. High risk categories mandate more aggressive and decisive treatment to prevent recurrences and also helps predict the prognosis for the patient.

1. Introduction

Basal Cell Carcinoma (BCC), first described by Jacob in 1827, is the most common cutaneous tumor, accounting for approximately 70% of all malignant diseases of the skin worldwide. Although the incidence of BCC is low in the Asian population when compared to Caucasians, the burden of the disease on the health care system may be high owing to a large population with a high absolute number of cases.[1–4]

Various authors describe many histological types of BCC, causing a lack of unified and accepted classification. The two important criteria used in classifying BCCs include histologic growth pattern and histologic differentiation, with the former having greatest biologic significance. An attempt at a simplified, accurate histologic classification of BCC based on histologic growth patterns is done in this study. This classification further paved way to the concept of risk typing BCC into low-risk and high-risk types. High risk types exhibit more aggressive behavior locally, higher

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rate of subclinical tumour spread and local recurrence along with a higher probability of incomplete excision. The primary goal of classification is to predict natural history, ie, high or low risk for recurrence and to effectively manage the patient. As the literature on BCC in India is scarce with lack of studies implementing risk typing, this study was undertaken with special focus on studying the tumor's biologic behavior, which correlates with its histologic growth pattern and risk typing. Furthermore risk typing guides current management of BCC. If the tumor subtypes are of high risk type, they usually require more decisive treatment.[5]

BCCs also need to be analyzed for their size, site, the frequency of its subtypes and the various factors which influence it, to develop and implement effective treatment strategies.[6]

2. Materials and Methods

The material for this retrospective study comprised skin biopsies of patients histopathologically diagnosed as BCC received in the Department of Pathology, over a timespan of eight and half years (2010-2018). Clinical details were collected; specimens were studied after fixation in 10% formalin. Representative areas were sampled and sectioned to obtain 5 micron thick paraffin sections. Microscopic findings of H&E stained sections were histopathologically studied, subtyped and further categorized into high and low risk types based on 'NICE Guidance on Cancer Services: Improving Outcomes for People with Skin Tumors including Melanoma (update): The Management of Low-risk Basal Cell Carcinomas in the Community May 2010'**.** IHC staining for BerEP4 was done in ten diagnostically challenging cases.

The data collected was entered in MS excel and analyzed using SPSS software version 16.0. The categorical variables were summarized using frequencies and percentages. Chi square test was employed for assessing the association between categorical variables. Fischer's exact test was used for checking association between categorical variables when the expected frequencies of more than 20% of the cells was below five. A p value below 0.05 was considered to be statistically significant. All the results are presented in appropriate tables and figures.

3. Results

A total of 91 specimens were received from 79 cases of BCC. 8 cases had both incision and excision biopsy, and in one case excision biopsy was followed by a recurrent lesion biopsied after 16 months. Two cases had biopsy from 3 and 2 sites respectively. High risk type of BCC (83.5 %) was more common than low risk type. The parameters used to risk categorize BCC is tabulated (Table 1). Of the 66 high risk cases, 63 were located in the facial region. There was significant association between location of the lesion and risk typing of basal cell carcinoma ($p<0.05$).

BCCs presented over a wide range of age from 8 years to 82 years, with a mean of 58 and 59 years for high risk cases and low risk cases respectively. Early development of BCC in high risk cases especially in sun exposed sites was seen in genetically predisposed patients. 3 cases of Xeroderma pigmentosa (XP) of ages 8, 10 and 22 years had basosquamous carcinoma (BSCC), a 38 year female with oculocutaneous albinism (OCA) had BCCs and BSCC & one 72 year old male patient with Nevus sebaceous (NS) had BCC.

A female preponderance was seen with an incidence of 65.15% in high risk BCC and 61.53% for low risk BCC respectively. Cephalic lesions, were more commonly seen, when compared to extra cephalic lesions with periocular region being the commonest site. High risk cases comprised of lesions in surgically difficult or cosmetically sensitive anatomical sites like periocular, nose, ear and lip regions.

Nodular BCC (30) was the most common subtype followed by the mixed type (19) in the high risk category. Of the 13 cases in the low risk group, 11 were of nodular type and one case each of fibroepithelioma of Pinkus and superficial type. Peripheral palisading and retraction clefts were identified easily and often seen, squamous differentiation was more commonly seen in low risk BCC. BCC was diagnosed only after multiple serial sections were taken in two cases. Perineural infiltration was seen in 04 cases and calcification was seen in 07 cases. A 65 year old male presenting with an ulcerated lesion on the dorsum of the foot showed BCC with osseous metaplasia. Of the 66 high risk cases, 44 has ulcerations as compared to 9 of the 13 low risk cases that did not have ulcerations. Ulceration was significantly associated with the risk typing of basal cell carcinoma. The other microscopic findings observed are as tabulated ($p=0.01$). (Table 2)

The majority of patients were referrals from general surgeons (34.6%), others were from ophthalmologists (28.2%), dermatologists (12.8%), plastic surgeons (7.6%) and otorhinolaryngologists (8.9%). 7.9% of patients had no documented referral source in the hospital notes.

4. Discussion

BCC is the most common skin cancer worldwide and constitutes a significant and costly health problem despite having low mortality rates. Although a significant variation in the incidence of BCC is noted depending upon ethnicity and geographic location, an increasing incidence is reported worldwide due to a larger amount of ultraviolet radiation reaching the earth's surface owing to the depletion of the ozone layer.[1–4] Although most studies report an increase in the incidence of BCCs,[7] we noticed an undulating trend with a steady increase in the number of cases between 2011 and 2013 and a peak rise in 2014.[8] Further, the number of

Table 1: Parameters used to risk categorize BCC

Parameters		High (66)	Low (13)	p value
Age (In years)	< 20	2	0	0.97
	21 – 40	5	0	
	41 – 60	29	6	
	61 – 80	28	7	
	>81	2	0	
Sex	Female	43	8	0.94
	Male	23	5	
Genetic predisposition	Present	5	0	0.68
	Absent	61	13	
Recurrence	Present	3	0	1.0
	Absent	63	13	
Margin Involvement	Present	19	0	0.06
	Absent	47	13	
Site	Face	63	6	**0.00**
	Neck	2	0	
	Trunk	1	4	
	Lower limbs	0	3	
Histologic type	Nodular	30	11	0.33
	Mixed	19	-	
	Infiltrative	9	-	
	BSCC	4	-	
	Superficial	2	1	
	Morpheic	2	-	
	FE of Pinkus	-	1	

Table 2: Microscopic features in BCC

Parameters		High (66)	Low(13)	p value
Solar elastosis	Present	5	0	0.68
	Absent	61	13	
Ulceration	Present	44	4	**0.01**
	Absent	22	9	
Regression	Active	62	12	0.68
	Absent	4	1	
Peripheral palisade	Present	66	13	1.0
	Absent	0	0	
Retraction cleft	Present	60	13	0.57
	Absent	6	0	
Pigment	Present	40	7	0.64
	Absent	26	6	
Ripple pattern	Present	4	0	0.82
	Absent	62	13	
*Inflammatory cells in stroma	L&P	61	12	0.82
	LF	1	1	
	M	3	0	
	Absent	1	0	
Stroma	Fibrosing	58	10	0.54
	None	8	3	
Squamous Differentiation	Present	22	5	0.97
	Absent	44	8	
Mucin	Present	3	0	1.0
	Absent	63	13	

*L&P: lymphocytes and plasma cells, LF: lymphoid follicle, M: macrophage

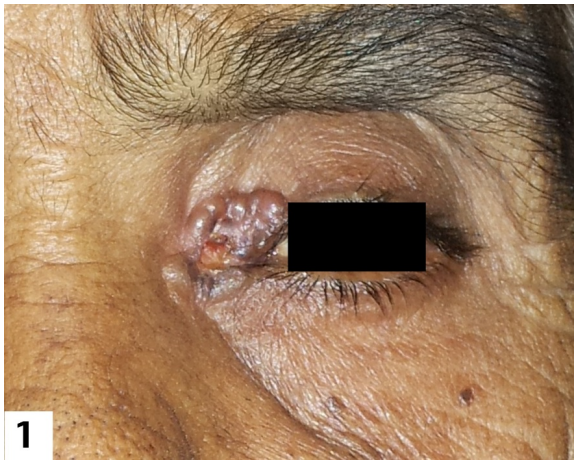

Fig. 1: 68 year old lady with a noduloulcerative lesion in the left periocular region.

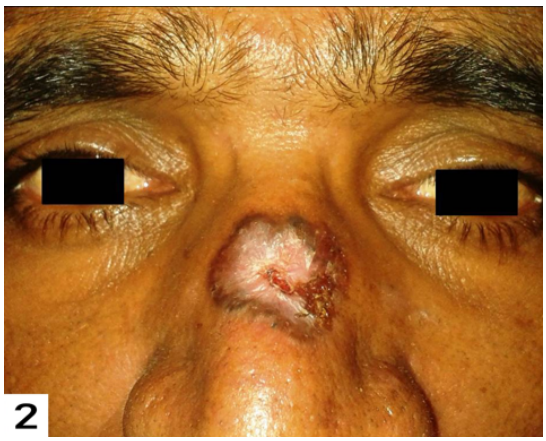

Fig. 2: An ulcerative lesion on the nose in an adult male patient.

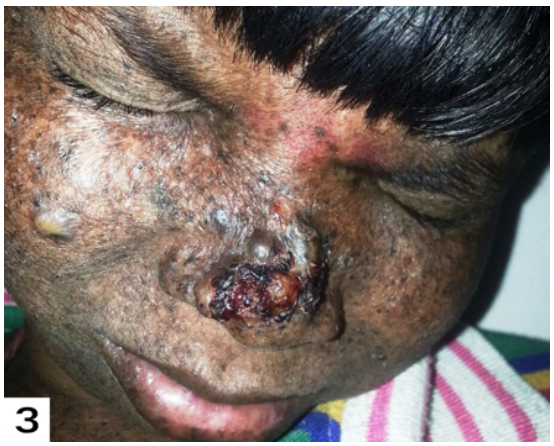

Fig. 3: Noduoulcerative lesion on the nose along with freckles over the face in a ten year old child with Xeroderma Pigmentosa.

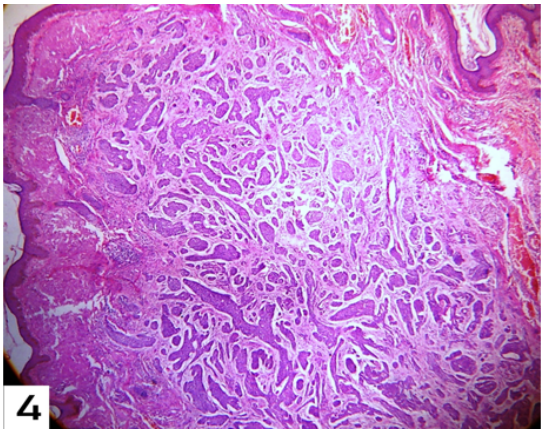

Fig. 4: Infiltrating type of BCC showing infiltrating nests and strands of basaloid cells (H&E 10X)

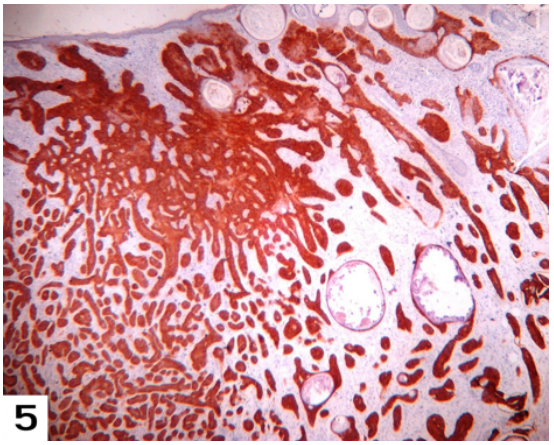

Fig. 5: BerEP4 staining in a case of BCC showing strong and diffuse membrane positivity. (BerEP4 10X)

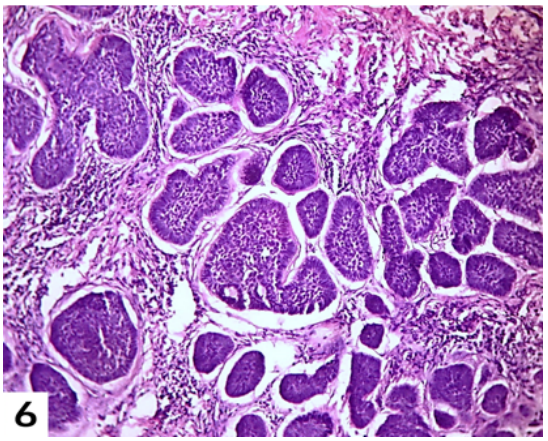

Fig. 6: Nodular BCC showing nests of basal cells with peripheral palisading and retraction clefts with stromal lymphocytic infiltrate. (H&E 40X)

cases reported decreased from 2015 to 2017 with small peak in 2018.[9] An uncertainity in the trend of cases reported may be attributed to changes in reporting practices or an actual increase in the number of cases, which highlights the need for cautious interpretation of data.[7,9–11]

The main aim of classification of BCC is to predict its natural history, i.e high or low risk for recurrence. There is an absence of uniform histological classification of BCC as there is a confusion whether to classify BCC based on growth pattern or histologic differentiation. A growth pattern based classification has been adopted by the Royal College of Pathologists in its minimum dataset for the reporting of skin cancersas it has the best correlation with tumour biology.[5,12–18] Clinical criteria for classifying cases into high and low risk types as outlined in the 'NICE Guidance on Cancer Services: Improving Outcomes for People with Skin Tumors including Melanoma (update): The Management of Low-risk Basal Cell Carcinomas in the Community May 2010' was implemented in this study.[17]

66 cases of BCC were classified as high risk and 13 cases as low risk BCC in our study. This risk stratification of BCCs based on growth patterns may help in uniform reporting with substantial agreement between dematopathologists.

The most commonly affected age group in this study was >60 years of age (45.56%) followed by 41-60 years, which closely resemble studies conducted in North India and Turkey.[1,6] A cumulative effect of ultraviolet radiation induced DNA damage and a decreased efficiency of DNA repair and immune surveillance mechanisms associated with aging may be the cause for increased incidence of BCC in older individuals.[1] 4 patients out of 6 that presented below 40 years of age had genetic diseases (3- XP and 1-OCA) predisposing them to develop BCC. One patient of XP had a sister with similar lesions.1 case of BCC in a 70 year old male had NS.

BCCs are more commonly seen in male patients as reported in many studies,[19] but we noticed an unusual female preponderance in our study which is consistent with the findings of another Indian study. Indian women especially those in rural areas are exposed intermittently to UVR as their main occupation is farming and due to cooking in open kitchens. A higher frequency of BCC noted in females in our study could be attributed to intermittent exposure to UVR which is implicated in the pathogenesis of BCC.[1]

Majority of the lesions in our study were found to involve the head and neck region (89.87%) with periocular (31.64%), nose (15.18%), cheek (15.18%), forehead (10.12%) and ear (8.86%) being the most commonly involved areas. These regions constitute the most central and prominent part of the head and neck region and are more prone to exposure to chronic sunlight. Most of our patients belong to this category probably as they are from rural areas who work during daytime as agricultural labourers. An embryologic role in the pathogenesis of BCC also has been hypothesized as there is a correlation between the common sites of occurrence of BCC and embryologic fusion planes in the head and neck area. The presence of embryological stem cells in clusters with special biology/ physiology along these fusion planes predisposing the development of BCC has been proposed.[8,20] The proportion of BCCs along these embryologic fusion planes were much higher (59.62%) than lesions at non cleft sites in our study.

Of the 123 periocular tumors studied in a period of 5 years (2011-2016), 23 cases were BCC, common in females (20 cases), and the most common age group was 60–69, ulcerated lesion being the most common presentation and 31.8% of the lesions were in the medial canthus. One patient showed a recurrent lesion 15 months following excision while another patient presented with three lesions, one involving the periocular region and other two involving the neck. Identification of lesions at the earliest can reduce the associated morbidity and recurrences.[21]

BCC in unusual sites which can be underestimated and be dangerous to patients deserve a special mention. 8 were located on covered / unusual sites of the body which includes three on the abdomen, two on the back and three on the lower extremity, which include the shin, ankle and foot.[22,23]

BCCs can exhibit a wide spectrum of histologic phenotypes, and upto 26 subtypes have been described.[24] BCCs have been traditionally classified based on differentiation patterns and clinical appearance like adenoid, keratotic, pigmented and so on although it holds no prognostic significance in most cases.[5] We attempted to simplify the histologic classification and hence used a histopathological classification combining both an assessment of the histological growth pattern and differentiation features. Eight types of growth patterns were recognized- nodular, superficial, morpheic, micronodular, infiltrative, mixed, BSCC and FE of Pinkus. A histologic type was assigned to each case, the pattern constituting more than 50 % of the tumor area or when it involved the invading part of the tumor and risk type was assigned after considering the clinical details of the patient. Superimposed on this classification was an assessment of differentiation. The presence of cystic, adenoid or keratotic features was considered as evidence of differentiation; otherwise tumors were classified as solid (undifferentiated). The most common subtype of BCC was nodular constituting 51.89% of the cases followed by mixed histologic type (24.05%). Importantly, all of the mixed subtypes contained a high risk histologic type.

Each subtype has an associated biological behavior that can affect the likelihood of tumor recurrence and treatment modality. Infiltrative, morpheic, BSCC and micronodular BCC are high risk histologic types and have a high

likelihood of incomplete excision and recurrence.

The exact classification of FE of Pinkus is debatable as some consider it as fenestrated variant of trichoblastoma while others consider it as a variant of BCC. A polypoidal lesion noted in a 46 year old male patient on the ankle, showed thin anastomosing strands of basaloid cells, two to three cells thick, surrounded by abundant stroma and terminated in nubbins of basaloid cells was diagnosed as FE of Pinkus and it was considered a low risk histologic type.[25,26]

BSCC a challenging rare tumour which lies between the two extremes of BCC and SCC needs to be differentiated from other cutaneous malignancies as it is aggressive, patients tend to have a poor prognosis due to higher rate of local recurrence and metastasis and require constant monitoring. Four cases of BSCC were seen in our study; three in patients with XP and one in a patient with OCA. The diagnosis of nonmelanoma skin cancer at an early age often conceals an underlying hereditary trait. It is of great importance in this part of the world to register these individuals early in life, educate them about the damaging effect of sun to prevent progression of premalignant lesions to malignant and detect and treat premalignant and malignant lesions early to reduce morbidity. Patients with high risk BCCs were younger when genetically predisposed and presented with larger, ulcerated tumors on cosmetically sensitive sun damaged skin that were incompletely excised in comparison to patients with low risk BCC.[26,27]

Majority (60.75%) of the high risk BCCs were ulcerated, 24.05% of them had positive excision margins and 6.3% of the cases were associated with solar elastosis. Histologically, low risk BCCs harbored a lymphocyte rich rather than plasma cell rich inflammatory infiltrate and showed more foci of active regression and stromal alterations of either a gain or loss of fibrosing tumor stroma. Features of old regression were not seen in both high and low risk categories. On comparing the histologic typing of incision and excision biopsies a concordance rate of 55.56% was noted in our study. A broad and deep incision biopsy specimen depicting the superficial and deep aspects of the tumour is imperative to accurately subtype BCC.[28]

BCC of all subtypes show strong and diffuse membranous staining for BerEP4 antibody. Epithelial membrane antigen (EMA) is negative in BCC and shows focal positivity in squamous and keratotic areas.[29] We performed BerEP4 staining on ten cases of BCC all of which showed strong and diffuse membranous staining.

There was metastasis in only one case in our study following three recurrences over a period of 7 years. Recurrence only was seen in two cases all of them involving the periocular region. Margin involvement was seen in both of these excision biopsies. The recurrent lesions were noted five years and one year and four months following primary excision in two patients and such information was not available in hospital records regarding the other patient. We are unaware of recurrences that could have occurred since the termination of the study.

5. Conclusion

BCC is a major health problem in a country like India owing to a large population. A simplified histological classification along with risk typing was done to achieve uniformity in reporting format among practicing Pathologists and to achieve substantial agreement between Pathologists and Dermatologists. Early diagnosis and treatment of patients is imperative to reduce morbidity among patients and thereby reducing financial burden of the disease overall. This study might help further guide other studies and also introduce health programs to help develop treatment, preventive and educational strategies to control BCC.

6. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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