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Histomorphological Spectrum of Basal Cell Carcinoma: Diagnostic Challenges andClinical Implications

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ABSTRACT: Background: Basal cell carcinoma (BCC) is a common nonmelanoma skin cancer seen usually on sun exposed areas in adults. Although these tumors generally do not metastasize, delay in diagnosis may result in disease progression and incomplete resection. A variety of neoplastic and nonneoplastic entities may be confused with BCC both clinically as well as histologically.

Aim & objective: To study the spectrum of histomorphological features in Basal cell carcinoma and to study the association of histological features with clinical features.

Methodology: The study included total 27 cases of histologically confirmed BCC over 24 months at GMCH Nagpur, Maharashtra. Various histological features were studied including clinical differential diagnosis.

Results:

Most of the lesions were located on face, but few other sites were also seen. Commonest clinical differential diagnosis was seborrheic keratosis and melanoma. In few cases, BCC was not clinically suspected. Histological features like arrangement of cells, nesting, retraction artifact, peripheral palisading and stromal mucinous change were commonly seen. Other features were also noted and discussed further with their association with clinical behaviour and other features**.**

KEYWORDS: Basal cell carcinoma, peripheral palisading, retraction artifact, seborrheic keratosis

I. INTRODUCTION:

Basal Cell Carcinoma (BCC) is the most common skin cancer worldwide. [1]Itsincidence is increasing by 10% every year. [2]It is more common in white skinned people than blacks. The frequency of BCC appears to be directly correlated with the degree of pigmentation in the skin, being most common in fair Caucasians and least common in African blacks.[3]About 74% of all non- melanoma skin cancers are basal cell carcinomas. [4]Apart from exposure to ultraviolet radiation, other risk factors include ionizing radiation, arsenic exposure, immunosuppression and certain inherited syndromes. [5]Basal cellcarcinoma is characterized by extensive local tissue destruction without metastasis and delay in the diagnosis and treatment can lead to morbidity due to local tissue destruction.[6]Clinically as well as histologically, it may mimic various other benign and malignant conditions leading to misdiagnosis. Although BCC is a slow growing tumour, some of its variants are more aggressive and are associated with increased morbidity. [7]Different clinical types generally reflect their respective histopathologic growth patternsand behaviour which necessitates the awareness of the morphological features and differential diagnosis of BCC. [8]Present study is a compilation of histologically confirmed cases of basal cell carcinomas mainly to study the morphological spectrum.

II. AIMS AND OBJECTIVES:

Present study is undertaken with following aimsand objectives:

1. To study the spectrum of histomorphological featuresof Basal Cell Carcinoma
2. To correlate histopathological features with clinical features and differential diagnosis of BCC on histopathology.

III. MATERIALS AND METHODS:

Following study is a descriptive cross-sectional study carried out in the department of pathology at Government medical college and hospital Nagpur, which is a tertiary health care centre in Maharashtra, central India. The study included all clinically suspected and histologically confirmed cases of BCC over two years duration from July 2017 to June 2019. It was approved by

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institutional ethics committee. The patients were attending dermatology or plastic surgery out patient department.

Inclusion and exclusion: Clinically suspected but histologically not confirmed as BCC were not included in the study. It included various types of samples like excisional biopsy, punch biopsy or wide local excision depending on the indication. In all cases, complete clinical information including age, site, symptoms, associated clinical features, other comorbidities, family history, personal and occupational history investigations done, and local examination findings including size, site, number, colour, appearance of the lesions including borders and other important features were noted. In each case, clinical differential diagnosis was also noted. The samples were processed using routine protocol after systematic gross examination and sectioning as per indication depending on the site, size of the lesion and type of surgery. E.g. surgical margins including base were sampled in cases of wide local excision. Multiple sections from the lesion/ growth were taken in order to study different morphological growth patterns.

Data was analysed by descriptive statistical methods such as percentage, mean, and other features. The study population comprised of 27 cases of histologically confirmed BCC.

IV. RESULTS:

We came across with total 27 number of cases of histologically confirmed BCC. Females slightly outnumbered males (F/M =11/16, F:M= 1.45:1). Most of the patients were above 50 years of age. However,four patients were from 30 to 40 years. Eldest patient was 80 years old. Except a case of 34 years old female who had multiple lesions over both extremities and trunk, all patients had single lesion. Commonest location was face, but other sites were trunk (chest), back, mons pubis and extremities. Table 1 shows the site wise distribution of the lesions. Various clinical differential diagnoses included seborrheic keratosis, melanoma, squamous cell carcinoma, DLE, xeroderma pigmentosum, porokeratosis, and keratoacanthoma. BCC was one of the differential diagnosis in all except two cases in whichBCC was not suspected clinically. The size of the lesions was ranging from 1 x 1 cm to upto 5 or 6 cm maximum. Figure 1shows the clinical appearances of the lesions at various locations. Figure 2 shows the spectrum of histological features in various cases. Table 2 shows the important histological features in all cases of BCC.

Table 1:

Serial no	Age (years)	Sex	Size (cm)	Site	Clinical diagnosis
1	70	M	3X3	Left cheek	Squamous cell carcinoma
2	72	M	2X2	Dorsum right hand	Keratoacanthoma, Nodular BCC, Seborrheic keratosis, Discoid lupus erythematosus
3	56	F	1.5X1	Near right eye	BCC
4	65	F	1X1	Right inner canthus	BCC
5	71	M	3X2	Upper back	BCC
6	69	F	1X0.7	Near right eye	Malignant melanoma, BCC
7	70	F	2X1.5	Left forehead	BCC
8	42	F	1X0.8	Left cheek	BCC, Melanoma
9	77	F	4X4	Right nose	Pigmented BCC
10	69	M	3X3	Scalp	BCC
11	38	F	2X2	Left lower eyelid	BCC
12	34	F	2X1	Bilateral upper limbs, lower limbs, trunk	BCC, Xeroderma pigmentosa
13	65	M	3X3	Nose	BCC
14	30	M	5X5	Chest	Adnexal tumor
15	50	F	4X2	Mons pubis	BCC

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16	30	F	1.2X1	Left cheek	BCC
17	69	M	2X2	Right ala of nose	BCC
18	72	F	2X1	Nose	Porokeratosis, Seborrheic keratosis, Discoid lupus erythematosus, Keratoacanthosis, BCC
19	79	M	2X1	Chest	Melanoma, BCC
20	56	F	1X1	Left side of face	BCC, Seborrheic keratosis
21	50	M	4X3	Left zygoma	BCC
22	31	M	1.5X1.5	Near right medial canthus	Pigmented BCC
23	68	F	2X1.5	Left popliteal fossa	Pigmented BCC, Melanoma
24	46	M	1X1	Nose	Noduloulcerative BCC, Pigmented BCC
25	73	F	3X3	Left ear	BCC
26	80	F	2X1	Left forehead	Pigmented BCC
27	50	M	3X3	Right nasolabial fold	BCC, Vascular tumor

Figure 1:

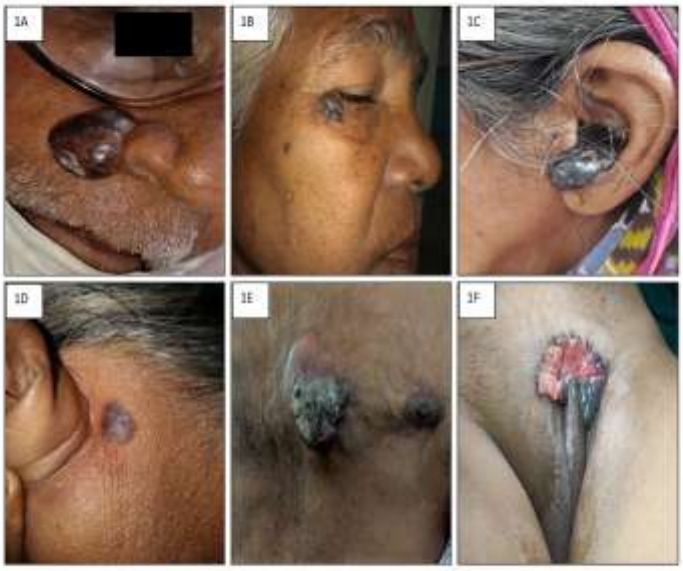

Figure 1: Clinical pictures: 1A- Clinical differential diagnosis was vascular tumor, 1B- BCC lateral canthus of eye, 1C- BCC external auditory canal, 1D- Superficial BCC, 1E- BCC chest wall, Clinical differential diagnosis was adnexal tumor, 1F- BCC Mons pubis

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Table 2:

Histological sub- type	No. of cases	Clinical characteristics / location	Presence of Pigment	Retraction artifact	Peripheral palisading	Mucinous change in the stroma
Nodular	15		12/15	13/15	+	14/15
Superficial	2	Behind ear, trunk	No	+	+	No
BCC with squamous differentiation	2	Face	1/2	+	+	No
Adenoid	2	Face (nose)	No	+	+	+
Keratotic	1	Face	+	+	+	No
Mixed	1	Ear	+	+	+	+
Others	4		3/4	2/4	+	4

Figure 2:

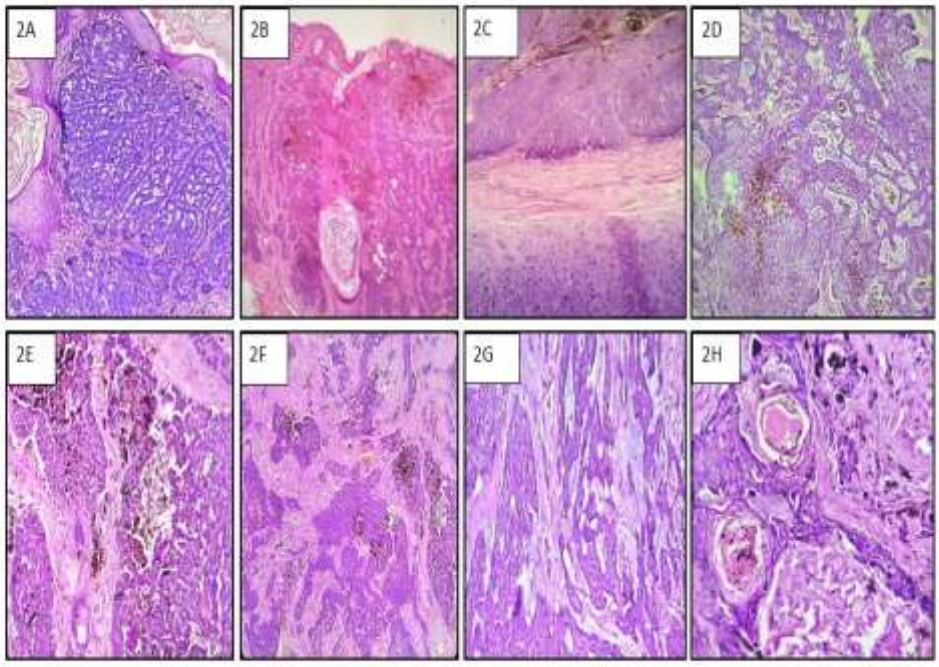

Figure 2: Photomicrographs: 2A- Micronodular BCC, 2B- Nodular BCC showing focal pigmentation,2C- Tumor mass separated from cartilage by fibrous septa, 2D- Peripheral palisading and artefactual clefting,2E- Necrosis and mitosis, 2F-Increased stromal collagen, 2G- Stromal mucinous change, 2H- BCC with squamous differentiation

V. DISCUSSION:

Although the incidence of basal cell carcinoma is low in India as compared to western countries, the number of cases is significant due to large population. Most of the studies on basal cell carcinoma are representing western incidence and

demographic profile. Present study is a descriptive cross -sectional study undertaken at Government Medical college and Hospital Nagpur which is a tertiary health care centre in central India, Maharashtra. This was mainly aimed to study the spectrum of histomorphathological features in histologically confirmed cases of basal cell carcinoma and also to see the association between various clinical features and histological features. It included 27 cases of basal cell carcinoma diagnosed over a period of two years. The patients' samples were mainly received from dermatology or plastic surgery department and occasionally surgery department. The type of specimen was either excisional biopsy (6/27, 22%), punch biopsy (12/27, 44%) or wide local excision(8/27, 30%) depending on the clinical presentation such as site, size and type of the lesion and clinical differential diagnosis. We found total 27 cases in two years duration which is a significant number as compared to other studies from India (29 cases in 5.5 years in a similar study from Kerala).[9]In our study, females outnumbered males (16/11, F:M=1.45:1) which is similar to above Indian study. Whereas Jina et al (2017) in their study mentioned male preponderance and related it to increased Sun and chemical exposure in males. [1] George et al mentioned that exposure to heat and fumes generated during cooking in kitchen may be a factor responsible for occurrence of basal cell carcinoma in females. Commonest location of the lesion was on the face (19/27) {on or around nose (5), eye (3),cheek (3), forehead(2), near canthus (2), other areas of face(2), ear (1)and scalp(1)}. Most of the available studies on BCC mention head and neck as the most common location (80%), other sites include trunk and extremities. We observed 8/27 (30%) cases of BCC on sites other than head and neck. These uncommon sites in our study were upper back (1/ M), dorsum of hand (1/ M), trunk multiple (1/F), mons pubis (1/F) and popliteal fossa (1/F). Although we saw one case on dorsum of the hand, it is mentioned as a very rare site for BCC. Such rare sites are more commonly mentioned in women. [11] Figure 1 shows clinical appearances of few lesions in our study. In cases of unusual sites andmultiple lesions are usually associated with distinct predispositionsis seen, and such patients are often younger and the tumors are on the trunk. [12] Wong CS et al have mentioned about recent increase in the truncal basal cell carcinomas, although the reason of this is not mentioned. [11]Certain inherited syndromes related with sonic hedgehog signalling pathway and germline mutations are associated with multiple BCC, young age of onset and association with other tumors and skeletal anomalies.[13]Various entities that can be clinically confused with basal cell carcinoma include nonneoplastic lesions like DLE, seborrheic keratosis, porokeratosis, benign neoplastic lesions such as adnexal tumors, dermatofibromas, keratoacanthoma, malignant tumors such as squamous cell carcinomas, melanoma, Merkle cell tumor and some preneoplastic lesions like Bowen's disease and xeroderma pigmentosum. In one of our case, clinical differential diagnosis was xeroderma pigmentosum. On histology, BCC was confirmed.Table 1 shows the list of clinical differential diagnosis in our study.Most common differential diagnosis were melanoma especially when the lesion is pigmented. Rarely BCC can be mistaken for DLE when the lesions of superficial BCC are associated with central atrophy and lack pearly borders. Lesions around nose and lips can also be confused with porokeratosis. Although in most of the cases, basal cell carcinoma was one of the clinical diagnosis. There were two such cases where BCC was not clinically suspected, one was adnexal tumour seen on chest and other was squamous cell carcinoma on cheek. Presentation on unusual site can miss BCC clinically as seen in case of tumor on chest wall from our study which was clinically mistaken for adnexal tumor. However,in a lesion on cheek,it was not clinically suspected as it was lacking typical features such as pearly appearance and eroded borders. A large nodular reddish brown tumor over nasolabial fold was clinically labelled as vascular tumor. (Fig 2A) Clinical resemblance of BCC to various neoplastic and non- neoplastic conditions can lead to misdiagnosis, hence the awareness of the morphological features and differential diagnosis of BCC is essential.[6]Similarly, on histology BCC may mimic various non- neoplastic conditions, benign adnexal tumors and other cutaneous malignancies. Table no. 2 shows the Gross appearance of the lesions and important histological features.

Varity of growth patterns seen in BCC can be broadly categorized into nonaggressive and aggressive based on their behaviour. Combinations of the growth patterns are also known. In general, superficial and nodular BCC show indolent behaviour, whereas micronodular, infiltrative, morpheaform variants show more aggressive behaviour. Angulated nests, presence of necrosis, brisk mitosis, decreased stromal retraction are indicative of more aggressive behaviour. [14] Similar to squamous differentiation, other differentiation such as towards sebaceous, clear cell are also mentioned in the literature, however we did not see any such feature except squamous differentiation.

[15]Apart from the stromal mucin, other stromal features included lymphocytic infiltration, prominence of fibroblasts and thick collagen.[6] In our study as shown in Table no. 2, peripheral palisading was the most consistent feature seen in all cases.Stromal mucin was seen in 21/28 (75%) cases, presence of pigment was seen in 18/25 (72%) cases, focal increase in stromal collagen was seen in two cases, focal lymphocytic infiltration was seen in 4 cases(Fig 2),two of them had ulceration over tumor surface. Perineural invasion was not seen in any of the cases we studied. Studies mention that pigment can be seen in many variants of BCC such as nodular, multifocal superficial, micronodular, and keratotic. Melanocytes were seen scattered throughout the tumor nests and melanophages were also seen in the stroma.[16] (Fig 2) We did not come across with any infiltrative or morpheaform variant and BCC with adnexal differentiation. As mentioned in literature, angulated nests were seen focally in some cases irrespective of the size of the tumor. The morphological features of BCC have strong prognostic association[16]. Clinical correlation,histological features and if required ancillary studies may be needed occasionally for arriving at definitive diagnosis of BCC. Characteristic diagnostic features include location of the tumor, arrangement of the cells, peripheral palisading, retraction artefact, presence of mitosis, apoptosis, pigment and stromal mucin.

Thus, in our study of 27 cases of basal cell carcinoma, nests and cords of basaloid cells in dermis, cell nests with peripheral palisading, stromal mucin, presence of pigment were the most consistent histological features. Additional features were presence of squamous differentiation, mitosis, apoptosis, necrosis, lymphocytic sprinkling and collagen deposition in stroma. In cases of typical clinical presentation, these features are sufficient for diagnosis of BCC.But in cases of atypical presentationslike multiple BCC, lesions at unusual sites,younger age at presentationand unusual histological features such as high-grade cytological atypia, extensive necrosis, lack of typical diagnostic features and specific variants,immunohistochemistry is helpful. [7] Complete workup for any associated features like inherited syndromes such as Gorlin- Goltz syndrome, xeroderma pigmentosum is required in such cases as their association with increased risk of BCC is known.[17]

VI. SUMMARY AND CONCLUSIONS:

In our study of 27 histologically confirmed cases of BCC, we have analysed various diagnostic histological features in different variants along with their associated clinical features. Knowledge regarding various histological features in typical and rare forms of BCC is essential for diagnostic confirmation and predicting tumor behaviour. Ancillary studies may be required in atypical cases.

CONFLICT OF INTEREST: None. Written consent was obtained for surgical procedures by corresponding department.

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