A clinicopathological insight of high-risk periocular basal cell carcinoma in a Central Karnataka tertiary care center

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Abstract

Introduction: Basal cell carcinoma (BCC) is a common example of basaloïd tumor accounting for approximately 70% of all skin cancers. Periocular skin and eyelids are common sites of neoplastic lesions of the head and neck. Even though BCC is a slowly growing tumor with no metastases, it poses a threat in the periocular region due to its closeness to vital structures.

Materials and Methods: The study comprised periocular BCCs diagnosed from July 2011 to June 2016. Clinical details were collected for the specimens. Microscopic findings were analyzed on hemotoxylin and eosin stained sections.

Results: Of the 123 periocular tumors in a period of 5 years, 27 were malignant epithelial tumors. Of these, 23 cases were BCC, common in females (20 cases), and the most common age group was 60–69 followed by 70–79 years. Most common presentation was an ulcerated lesion and 31.8% of the lesions were in the medial canthus.

Conclusion: All our cases were periocular lesions, so they were of high risk. Two patients were genetically predisposed and younger than 40 years, and two patients had recurrences. The referral patterns will be influenced by the concept of risk type (low or high) for BCC. Identification of lesions at the earliest can reduce the associated morbidity and recurrences.

Introduction

Basal cell carcinoma (BCC) is a common example of basaloïd tumor accounting for approximately 70% of all skin cancers. The term “BCC” is derived from its resemblance to epidermal basal layer or developing follicular germ layer. BCC occurs often on the face which is an area of heavy sun exposure and has numerous sebaceous glands.

Periocular region is defined as the area bordered by the eyebrow above and the midface below excluding the circumscribed area of the intervening eyelids.¹ Periocular skin and eyelids are common sites of neoplastic lesions of the head and neck. BCC is unevenly distributed around the eye.²

Even though BCC is a slowly growing tumor with no metastases, it poses a threat in the periocular region due to its closeness to vital structures. Most are easily diagnosed, they can exhibit a spectrum of histologic types, and their similarity to other cutaneous neoplasms, both benign and malignant, can make diagnosis difficult.³

Materials and Methods

The material for the study comprised of periocular BCCs diagnosed in the Department of Pathology, JJM Medical College, Davangere, from July 2011 to June 2016. Specimens were received from hospitals in and around Davangere in Central Karnataka.

Clinical details were obtained from the histopathology requests. Formalin-fixed specimens were sampled, and microscopic findings were analyzed.

Results

In the study period of 5 years from 2011 to 2016, of the 123 periocular tumors, 27 were malignant epithelial tumors. Of these, 23 cases were BCC, three cases were squamous cell carcinoma (SCC), and one was keratoacanthoma.

BCC was common in females (20 cases) and 60–69 years age was the most common age group and then 70–79 years.
The most common presentation was an ulcerated lesion in 21 (91.3%). Of the 48 high-risk cases of BCC (unpublished data) in the head and neck region in the study period of 5 years, 23 (47.9%) were in the defined periocular region. 20 cases of these were from the ophthalmology department and three from the surgery department.

In our study, majority of the lesions were in the medial canthus (31.8%), followed by lower eyelid (27.2%), upper eyelid (17.4%), and others (23.6%) [Figure 1].

Nineteen of the 23 cases had undergone excision biopsy with margin clearance in 17 cases. In two cases, location in medial canthus rendered trouble in margin clearance, and they later came back with recurrence. Three cases had undergone incisional biopsy, one of whom was a neglected destitute woman with maggots in the ulcer and debridement was done. Other two cases were lost to follow-up, and hence, no excision biopsy was performed. In a 22-year-old female patient of xeroderma pigmentosum (XP), exenteration was performed due to deep orbital extension of eyelid BCC.

Histologic types of BCC included mixed (11), infiltrative (6), nodular (3), morphoeic (2), and micronodular (1). Additional microscopic features seen were pigmentation (13/23), ulceration (20/23), solar elastosis (8/23), retraction cleft (11/23), peritumoral lymphocyte infiltration (19/23), stromal fibrosis (17/23), stromal mucin (1/23), ripple pattern (2/23), and squamoid differentiation (7/23) [Figure 2].

Two cases had recurrence which was confirmed on histopathology. One, a 68-year-old female, had recurrence twice in the next 2 years. The other, a 49-year-old male, had recurrence after 3 years. In both the cases, the initial lesion was in the medial canthus, the site with high risk for recurrence.

Discussion

Annually >700,000 new cases of skin carcinomas are diagnosed, of which 77% are BCCs.[4] In India, skin cancers are 1–2% of all cancers and incidence is lower than western countries probably due to melanin protection, but they are on the rise in India also. The large population contributes to a significant increase in an absolute number of cases. In India, SCC of skin is more common than BCC which is the commonest skin cancer in the world.[5]

BCC, a classical basaloid neoplasm, is the most common of all cutaneous malignancy in hair-bearing region. The current management is determined by its natural history, i.e., risk for recurrence and its histologic growth pattern which decides the tumor behavior. The mortality is low as it rarely metastasizes, but morbidity is high and also with its increasing incidence all over the world, BCCs are a burden on health services.[6]

Appearance and behavior of many skin neoplasms in the periocular region may be unique due to the peculiar features of eyelid skin and adnexal elements. Many of them are benign, but to rule out malignancy, often the ophthalmologist will request tissue microscopic examination.[9] Of all the skin malignancies treated, only a small percentage is in this region with wide variation among varying population, but they are challenging and late diagnosis needs extensive surgery with poor esthetics. The environmental factors such as sunlight (sun protected and sun exposed) and ultraviolet exposure and genetic factors such as pigmentation and genodermatoses have an impact on geographic variation, biology, and morphology in these locations.[8-10]

Our study is from a geographical location with sunlight exposure having an impact on the periocular location of these tumors. Our college hospital is a tertiary referral center in Central Karnataka in South India for the surrounding districts with a significant rural population. Hence, the task was undertaken of documenting the high-risk cases of BCC by multidisciplinary approach.

In general, BCCs occur in the fourth decade and beyond, with exceptions, particularly in the background of specific genodermatoses or immune compromise.[11]

Twenty of 23 cases of BCC were female patients in our series. The female predominance may be explained by the increasing proportion of women among the elderly in our area where cardiovascular diseases and internal cancers are reasons for high mortality in men.
In the series of 5504 excised neoplastic eyelid lesions, BCCs were 14% of all lesions and 86% of malignancies. BCCs represent 18.6% of all our periocular cases (123 cases) and 85.1% of malignant epithelial tumors (27 cases), a figure that does not compare with Asian series where BCC accounts for only one-third of eyelid cancers.

In a study from the Philippines, BCC and sebaceous gland carcinoma (SGC) were the most frequent malignant tumors of the eyelid (30.6%) and were seen in women slightly more often than in men. SCC, melanoma, and lymphoma were the next three among the top five. All together accounted for 96.6% of the malignant eyelid tumors. BCC and melanomas were often seen in the lower lid, while SGC and SCC were more often in the upper lid. In our study of 123 periocular tumors, of the 27 malignant eyelid tumors, 12 were SGC, 11 BCC, 2 SCC, and one case each of keratoacanthoma and melanoma.

BCC was the most common malignant eyelid tumor, with 67% of lesions occurring on the lower lid and 10% at the inner canthus. SCC, in contrast, represented only 2% of lesions and rarely occurred on the eyelid. The ratio of BCC to SCC of the eyelids was 30:1. A total of 124 BCC tumors were on the lower lid (76.5%), 25 on the upper lid (15.4%), 11 at the medial canthus (6.8%), and 2 at the lateral canthus (1.2%) in a study from the United Kingdom. In our study, 31.8% of tumors were in the medial canthus, followed by 27.2% in the lower eyelid, 17.4% in the upper eyelid, and others (23.6%), and the ratio of BCC: SCC was 7:6.1.

Literature on clinicopathological features of BCC in India is scant and does not explore the pathogenesis. Often BCC occurs on sun-exposed skin, but its occurrence in sun-protected areas such as the inner canthus may be related to bio-embryological closure of skin creases. A higher proportion of BCCs (70.17%) in the sites of congenital clefts in the head and neck than in the non-cleft sites supports the hypothesis of the existence of embryonic stem cell clusters along these lines and their role in pathogenesis. An exceptional biology/physiology in these sites of congenital clefts may predispose these sites to develop BCC. In our unpublished department data of 9 years, of 78 cases of BCC, 73 cases were in the head and neck supporting the role of bio-embryological closure of clefts in its pathogenesis and only 5 extracephalic cases were seen.

Our results were compared with Kale et al. study of common eyelid malignancies from plastic surgery department where the exact location in the lower eyelid is not mentioned. On comparison with Malhotra et al. medial canthus was the most common location in our study [Table 1].

In a study of BCC in the North Indian population, 91.2% of the 34 lesions were in the sun-exposed region of the head and neck and with a male predominance. Cases were across in a wide age range, but highest number was in 40–60 years of age.

A significant number of tumors at the medial canthus were seen by Morris et al. and other Mohs micrographic surgery studies because this is a critical site where tumors are difficult to excise completely and recurrence often leads to orbital and/or bony invasion and the risk of them requiring exenteration.

Large-scale review of BCC and analyses in other than White population including histopathological features are not available except in 243 Japanese patients and 78 Korean patients, where 75–85% occurred in the head and neck.

Information about the behavior of a tumor and classifying BCC into risk groups according to NICE guidance on cancer services help the clinician for further treatment plan and dispensing of the patient. The notion of high and low risk for BCC will become important because this will determine recommendation for primary and/or secondary care. All our 23 cases were of high risk as they were periocular lesions. In addition, among our genetically pre-disposed patients, an XP case was younger than 24 years and another patient was 40 years with ocucolutaneous albinism (OCA), and two patients had recurrences.

The histological subtyping is complicated by a broad diversity of described histopathologic phenotypes, inconsistent nomenclature, imprecise definitions, admixture of multiple subtypes within a single tumor, and incisional sampling. Histopathological examination is required to distinguish BCC from its clinical mimics such as other ulcerative lesions, nevi, actinic keratosis, and trichoepithelioma.

In our study, we used a histopathological classification combining both an evaluation of the growth pattern and differentiation features. Eight types of growth patterns were recognized. A histologic type was assigned to each case with the pattern constituting >50% of the tumor area and risk type was assigned considering the clinical details also. Of the total cases examined, 11 cases (45.82%) were BCC of mixed histological subtype, the predominant variant in our study. Importantly, all of the mixed subtypes contained a high-risk histologic type of morphea, micronodular, and infiltrative.

The histological growth pattern used in the creation of the idea of low-risk and high-risk types of BCC is of secondary importance. High-risk types are characterized by more chances of subclinical spread, incomplete excision, and aggressive behavior with more frequent local recurrences. The cell differentiation criteria are not reproducible and have led to more than 20 architectural and cytological subtypes. More than one subtype is seen in many BCCs with no agreement on the proportion of individual types to categorize a new variant. Hence the support for classification based on cell type is diminishing.

Epithelial-stromal interaction to gain a permissive environment probably involves the evolution from low risk to high risk. Solar elastosis was seen in 31% of low-risk recurrence

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**Table 1: Comparison with other studies**

<table>
<thead>
<tr>
<th>Features</th>
<th>Kale et al. [17]</th>
<th>Malhotra et al. [18]</th>
<th>Present study</th>
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<tr>
<td>Median age/range</td>
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<td>40–60</td>
<td>65</td>
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<tr>
<td>Females (%)</td>
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<td>62.5</td>
<td>86.36</td>
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<td>Common site</td>
<td>Lower lid</td>
<td>Medial/lateral canthus</td>
<td>Medial canthus</td>
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<tr>
<td>Cases (n)</td>
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<td>34</td>
<td>23</td>
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Periocular BCC Chatura, et al.  
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Chatura, et al.
and 52% of high-risk recurrence. A loose fibromyxoid peritumoral stroma was evident in 76% of all tumors. Squamous differentiation was found in 17%. Among the subtypes and in individual cases, the host inflammatory response was varied.[25] In our study, solar elastosis was seen in 34%, fibromyxoid peritumoral stroma in 78%, variable peritumoral lymphocyte infiltration in 82%, and squamoid differentiation in 30%.

Clinically, the diagnosis is usually straightforward as in our series, in which <1% of BCCs were misdiagnosed as either seborrheic warts or cysts when central necrosis was marked. Although the exactness of the clinical diagnosis of BCC is important, there is little published data. Schwartzberg et al., using a questionnaire, documented the confidence of clinical diagnosis of BCC among dermatologists at the University of Miami.[36]

The positive predictive value (PPV) and sensitivity for the clinical diagnosis of excised BCC were 72.8% and 63.9%, respectively.[27] In our study, the PPV was 80%, and sensitivity was 90.9%. The sensitivity varied with body site and was highest for BCCs on the head and neck. When further analyzed according to the type of surgery, PPV and sensitivity were significantly higher for the wide local excision than for punch or incision biopsy.[28]

BCCs rarely metastasise as they are stroma dependent and cannot survive when transplanted to sites free of dermal tissue.[23] We had no cases with metastases in our series of periocular cases and also in the unpublished data of 78 BCCs which included other sites.

The contiguity of eyelid with vital structures such as cranium makes BCC a danger although it is a slow-growing and non-metastasizing neoplasm.[19] BCC is locally aggressive and always follows the path of least resistance and so, when it encounters bone, cartilage, or muscle, it does not invade them but spreads along the periosteum, perichondrium, fascia, or tarsal plate. This pattern of spread makes management difficult in the periocular region where embryonic fusion plates favor tumor penetration also. Recurrence is higher in the inner canthus than at other sites due to spread along these planes, and hence, there is extensive subclinical tumor which is underestimated and this is recognized as the “tip of the iceberg” phenomenon. As reconstruction is difficult in this area, many times, excision is inadequate and results in serious morbidity.[3] Since recurrences appear a few years after treatment, follow-up should be endured for at least 5 years. Patients had recurrences after 3 years and 2 years in two cases.

Recurrence of periocular lesions is high when surgical excision margins are not scrutinized. A benefit of observing for tumor recurrence is that new lesions which develop subsequently and patients are unaware can be identified.[13]

Eyelid BCCs which were advanced or recurrent were the most common presentation in patients who underwent exenteration in a referral center which could have been avoided if they had been treated earlier.[10] In our study, we had only one exenteration as all others were treated early with excision.

In the first decade, genodermatoses patients usually develop oculocutaneous malignancy such as BCC and SCC as opposed to others who develop such malignancies later in the fifth or sixth decade.

**Figure 3:** (a) Xeroderma pigmentosa patient with lower eyelid lesion. (b) Oculocutaneous albinism patient with lesion in lateral canthus

Eyelid skin, such as facial skin, is associated with the typical changes of genodermatosis. Sun exposure is similar to that of facial skin which explains the higher frequency of malignancies involving these areas. BCC is the most common malignancy diagnosed by ophthalmologists, and 86.9% of our cases were from ophthalmology department.

Two patients with genodermatoses had BCC although SCC is the most common malignancy reported in them. [Figure 3] One OCA patient had two lesions diagnosed as BCC. The patient underwent wide excision of all lesions with margin clearance but was lost to follow-up. Another female patient aged 22 years with BCC underwent excision along with exenteration of the eyeball with margin clearance and is under follow-up with no recurrence. Her sibling had cutaneous lesions of XP. In a series of patients with genodermatoses, a diagnosis of BCC was made in cases involving the lower eyelid and lateral canthus.[29]

A diagnosis of BCC in the young is delayed and treatment was also delayed as both the patient and physician are not willing to believe that it can occur. Two groups of patients emerge in the young, one with UV light injury and other with family history.[30]

**Conclusion**

The rising incidence of periocular cancers in India constitutes an important costly health issue. Periocular region is an important part of the entire head and neck region exposed to chronic sunlight in most of our rural population comprising both men and women who are daytime agricultural workers and, hence, at high risk for BCC. Detection and treatment of periocular BCCs can meaningfully decrease the morbidity, secondary invasion, and recurrences.

**References**
