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Detection of Basal Cell Carcinoma–a Guide Line for General Practitioners in Dentistry

Rania E. Elsherbiny[1], Ayesha Umair[2], S. N. Azzeghaiby[3], Ibrahim Alzoghaibi[4], Said Dabour[5] and Bassel Tarakji[6*]

[1]Department of Biomedical Sciences, Alfarabi College of Nursing and Dentistry, Saudi Arabia.
[2]Department of Oral and Maxillofacial Sciences, Al Farabi College of Nursing and Dentistry, Riyadh, Saudi Arabia.
[3]Department of Oral and Maxillofacial Sciences, Kingdom of Saudi Arabia, Riyadh, Saudi Arabia.
[4]Department of Restorative Dental Sciences, Dean of Alfarabi College of Dentistry, Kingdom of Saudi Arabia, Riyadh, Saudi Arabia.
[5]Department of Biomedical Sciences, Alfarabi College of Nursing and Dentistry, National Institute, of oceanography and Fisheries, Cairo, Egypt.
[6]Department of Oral Maxillofacial Sciences, Alfarabi College of nursing and Dentistry, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration between all authors. Author REE designed the study, performed the statistical analysis. Authors AU, SNA and IA wrote the protocol, and wrote the first draft of the manuscript. Authors AU and SD managed the analyses of the study. Author BT managed the literature searches. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Basal cell carcinoma or BCC, is a malignant epithelial tumor of the skin, usually seen in the head and neck. Most BCCs are slowly growing and behave in a relatively benign, nonaggressive fashion, but a few of them grow rapidly and infiltrates the structures beneath the skin. Because dentists routinely evaluate the head and neck region, this review will help and guide the oral health care providers to diagnose basal cell carcinoma at an initial stage and provide early treatment by referring them to oral and

**Corresponding author: Email: denpol@yahoo.co.uk;*

maxillofacial surgeons, hence reducing the morbidity rate and treatment cost. A literature search using MEDLINE, accessed through the National Library of Medicine Pub Med interface, for articles relating to Basal cell carcinoma etiological factors, clinical features and its diagnosis written in English language were accessed. This study has a specific focuson early detection of BCC which is mostly located in head and neck region. Theskin tumors which are located in other part of the body were excluded from this study. Studies describing cohort, case series and miscellaneous clinical reports were retrieved and evaluated from 1993 to 2013.

Keywords: Basal cell carcinoma; head and neck; dentists; early detection.

1. EPIDEMIOLOGY

In 1827 the term “rodent ulcer” was used to describe what we now know as a basal cell carcinoma (BCC) [1]. It is named as basal cell carcinoma due to the resemblance of the epithelial tumor cells to normal basal cells of the skin. BCC is a locally aggressive tumor arising from the basal layer of the epidermis and its appendages and is the most common skin malignancy [2,3]. According to research about two thirds of the tumors are located in the head and neck region which are mostly exposed to the sun [4]. For the past 10 years the incidence of basal cell carcinoma has been increased considerably [5].

In 2006 more than two million nonmelanoma skin cancers were treated in the United States, of which the majority were BCC [6]. A population-based study reported that approximately 3.5 million nonmelanoma skin cancers were treated in the United States during the same year [7]. Further, an incidence-based mathematical model supports a high prevalence of nonmelanoma skin cancer in the United States [8]. In 2007, about 13 million white non-Hispanic individuals in the United States have had a personal history of at least one nonmelanoma skin cancer. Studies have shown that approximately 40 percent of patients having BCC will develop another lesion within the following span of five years [9,10]. This indicates that the individuals with a history of BCC are at a higher risk for developing subsequent lesions.

BCC is mostly observed in people who are light-skinned (type 1 or type 2 skin) and it rarely affects the dark-skinned individuals. Type 1 skin individuals are very fair and have red or blond hair and freckles; such people always burn and never tan. Whereas, type 2 skin are fair and can burn easily at the same time tanning minimally. Research has shown that the incidence is low in blacks, Asians and Hispanics whilst whites individuals of Celtic ancestry have the highest risk for developing BCC [11].

Men are affected twofold as women, it may be due to the fact that men are exposed to sun more due to their increased recreational and occupational activities. Currently male-to-female ratio is approximately 2.1:1 respectively. It is reported that the incidence of BCC involving the periocular skin are equal in men and women in [12]. Further studies have shown that the age-adjusted incidence rates for all types of malignant tumors of the eyelid in men and women were 19.6 cases and 13.3 cases respectively, per 100,000 populations per year. Whereas the incidence rates specifically for BCC of the eyelid for men and women were 16.9 and 12.4 cases respectively per 100,000 populations per year [12].

There is a prominent global variations in the incidence rate of BCC, geographic deviation plays a major role. States that are closer to the equator have two fold incidence rate of BCC as compared to Midwestern United States [13,14]. Finland, a northern European country have one-fourth the incidence rate of the Midwestern United States. This contrasts with Australia where rates are 40 times that of Finland [15-17].

With aging the incidence of BCC also increases; individuals of age 55 to 75 have almost 100-times higher chance of developing BCC than individuals younger than 20years of age [18]. Although increasing longevity may underlie some of the increasing incidence of BCC, the incidence of BCC particularly among American women younger than 40 years of age also appears to beraised [19].

Individuals with Nevoid basal cell carcinoma syndrome (NBCCS), are predominantly at a higher risk of developing a common non-life-threatening form of non-melanoma skin cancers. This Syndrome also known as basal cell nevus syndrome, multiple basal cell carcinoma syndrome, Gorlin syndrome, and Gorlin–Goltz syndrome, is ahereditary medical condition involving multisystem deficiency such as the skin, nervous system, eyes, endocrine system, and bones. About 10% of people with this condition are not likely to develop basal cell carcinomas (BCCs) [20]. NBCCS is an autosomal dominant condition causing unusual facial appearances and a predisposition for basal cell carcinoma [21]. The prevalence is reported to be 1 case per 56,000-164,000 population. Recent work in molecular geneticshas shown NBCCS to be caused by mutations in the PTCH (Patched) gene found on chromosome arm 9q [22].

2. CLINICAL PRESENTATION

BCC occurs mostly on the face, head (scalp included), neck, and hands. The characteristic features of BCC tumors include the following: [23]

- Waxy papules with central depression
- Pearly appearance
- Erosion or ulceration: Often central and pigmented
- Bleeding: Especially when traumatized
- Oozing or crusted areas: In large BCCs
- Rolled (raised) border
- Translucency
- Telangiectases over the surface
- Slow growing: 0.5cm in 1-2 years
- Black-blue or brown areas

Cases reported according to occurrence of BCC on specific location such as; On the head (mostly on the face; most frequent location is the nose, specifically the nasal tip and alae)-70% [24], on the trunk-25% [25], on the penis [26], vulvaor perianal skin 5% [27,28].

BCC is a locally invasive and slow-growing, non-melanoma skin cancer (NMSC) that rarely metastasizes. If left untreated, BCC can cause considerable morbidity by infiltrating the underlying cartilage, muscle and bone. Sun-exposed areas of the head and neck are most frequent sites, although any cutaneous hair-bearing surface can be affected [29]. BCCs are often asymptomatic, but can be sore or itchy. If ulcerated, they may bleed with minimal trauma. Elderly patients usually present late with large, symptomatic, crusted lesions, only seeking help when the area involved becomes troublesome. BCC is classified by their

clinical and histopathological appearance, and risk factor depends on the location where they have arisen [30].

Approximately 70 percent of BCCs occur on the face, consistent with the etiologic role of solar radiation (UV light). 15% present on the trunk and only rarely is BCC diagnosed on areas like the penis, vulva or perianal skin [31].

BCC can be divided into three groups according to their clinical presentation and based upon lesion histopathology: (1) nodular (2) superficial (3) morpheaform.

The Nodular BCCs typically present on the face as a pink colored papule as shown in Fig 1. It represents about 60 percent of cases. The lesion usually appears as pearly or translucent and a telangiectatic vessel is frequently seen within the papule. Frequent ulceration are seen therefore the term "rodent ulcer" refers to these ulcerated nodular BCCs. Nodular basal cell carcinoma is shown in.

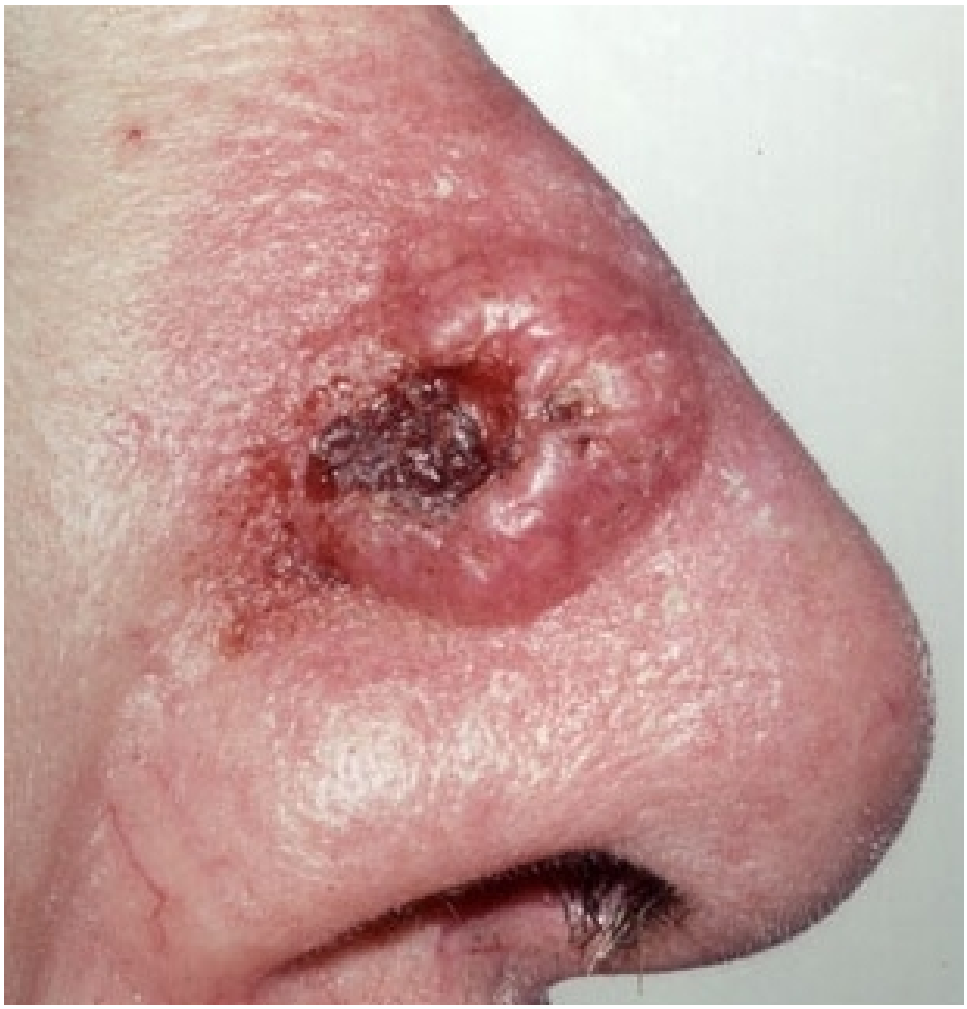

Fig. 1. Nodular or noduloulcerative basal cell carcinoma, the most common type, showing central ulceration

About 30 percent of BCCs are Superficial BCCs. They present as slightly scaly, non-firm macules, patches or thin plaques light red or pink in color, mostly occuring on the trunk [31]. The centrally the lesion shows an atrophic appearance whereas the periphery is usually rimmed with fine translucent papules. Upon illumination the shiny quality may be evident. Rarely, brown or black pigmentation may be present, which may cause difficulty to differentiate it from melanoma. Superficial BCCs is slowly growing, usually asymptomatic and can vary considerably in size measuring from a few millimeters to lesions as big as several centimeters in diameter or more if left untreated. The morpheaform orsclerosing BCCs comprise 5 to 10 percent of BCCs. These lesions are typically smooth, flesh-colored, or very lightly erythematous papules or plaques that are frequently atrophic; they usually have a firm or indurated quality with ill-defined borders, as shown in Fig. 2.

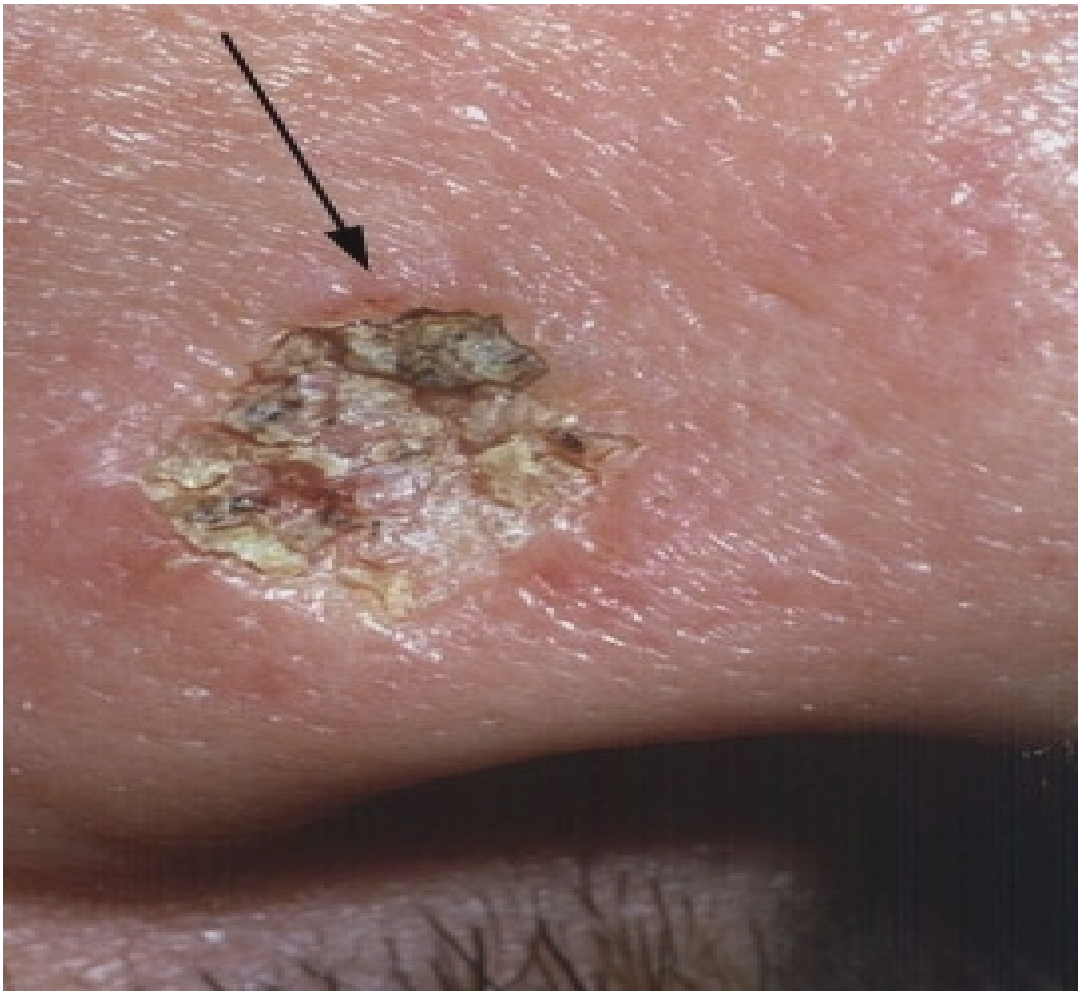

Fig. 2. Sclerosing type of BCC, with irregular borders

Morpheaform, infiltrative form and micronodular are grouped as "aggressive-growth" BCC [31]. Infiltrative and micronodular subtypes are less common than the morphea form BCC. Basosquamous cell carcinoma probably best classified as a squamous cell carcinoma is yet another subtype is which is an aggressively behaving rare tumor. Nodular and superficial

BCCs can produce pigment therefore are referred to as pigmented BCCs. Some lesions can have a mixed histology hence showing features of multiple histologic subtypes. Quite a few rare syndromes have been described that present with multiple BCCs, among them the most common is Gorlingoltz syndrome. Bazex syndrome is another rare disorder characterized by follicular atrophoderma andmultiple BCCs [32]. Rombo syndrome presents with atrophoderma vermiculatum and vellus hair cysts with milia-like appearance. Patients with xeroderma pigmentosum are at increased risk for BCC as well as squamous cell carcinomas and melanomas. The incidence of these malignancies for individuals under the age of 20 is approximately 2000 times that seen in the general population [33].

3. HISTOLOGIC FINDINGS

BCC comprises of two categories depending on their histological basis: undifferentiated and differentiated type. BCC with slight or no differentiation is referred to as solid BCC. It includes pigmented BCC, superficial BCC, sclerosing BCC and infiltrative BCC. Where as the differentiated BCC often shows differentiation toward cutaneous appendages, such as hair (keratotic BCC), sebaceous glands (BCC with sebaceous differentiation) and tubular glands (adenoid BCC). Noduloulcerative (nodular) BCC is mostly differentiated type [34-37]. Histological types of BCC are described in detail in Table 1 [35-37].

Table 1. Histopathological features of BCC

Type		Description
1.	Nodular basal cell carcinoma	Nodular or noduloulcerative basal cell carcinoma, the most common type, generally consists of large, round or oval tumor islands within the dermis, often with an epidermal attachment. The solid (nodular) type accounts for approximately 70% of all cases. Artificial retraction of the tumor islands from the surrounding stroma is commonly seen. Ulcerations may be seen in large tumors.
2.	Micronodular basal cell carcinoma	aggressive variant, micronodular BCC, appears as small, nodular aggregates of basaloid cells
3.	Pigmented basal cell carcinoma	In pigmented basal cell carcinoma (BCC), benign melanocytes in and around the tumor produce large amounts of melanin. These melanocytes contain many melanin granules in their cytoplasm and dendrites
4.	Adenoid basal cell carcinoma	The adenoid type consists of strands of basaloid cells in a reticulate pattern, frequently with prominent stromal mucin. It may occur with the solid type.
5.	Morpheaform (sclerosing) basal cell carcinoma	The more aggressive morpheaform BCCs have growth patterns resulting in strands of cells rather than round nests, within a fibrous stroma. They constitute approximately 5% of BCCs. Morpheaform

		BCC arises as thin strands of tumor cells (often only 1 cell in thickness) that are embedded in a dense fibrous stroma. The morpheaform basal cell carcinomas exhibit islands of tumor extending into the tissue and may exhibit perineural invasion in 3% of patients. This finding helps classify these 2 histotypes as the most aggressive, with the highest rates of recurrence and positive margins after excision.
6.	Infiltrative basal cell carcinoma	This type of BCC accounts for 10% of BCCs. Tumor cells have growth patterns resulting in strands of cells infiltrating between collagen bundles rather than round nests. The strands of infiltrating BCC tend to be somewhat thicker than those seen in morpheaform BCC, and they have a spiky, irregular appearance.
7.	Cystic basal cell carcinoma	Cystic basal cell carcinoma consists of large, round or oval tumor islands within the dermis with mucin present in the center of the island. This space is caused by central tumor cell degeneration.
8.	Superficial basal cell carcinoma	The (multifocal) superficial type (see the image below) is characterized by numerous small nests of tumor cells usually attached to the undersurface of the epidermis by a broad base. Approximately 10-15% of all BCCs are of this type. This is the most common pattern seen in BCCs of the shoulder

4. CASES PRESENTING BASAL CELL CARCINOMA IN ORAL CAVITY

It is very rare to find a case of true basal cell carcinoma (BCC) involving the oral mucous membranes. Mostly the lesions occurring in the oral cavity involving the gingiva are peripheral ameloblastomas and not true BCCs. In 2001 Del Rosario et al. [38] presented a true BCC case, which arose on the buccal mucosa of a 69-year old man. A 1.3cm ulcerated plaque without gingival connection was seen. The lesion exhibited classic histological features of BCC presenting palisading and retraction spaces and focal communication with the overlying squamous epithelium. The anatomical location, focal squamous (metatypical) features, and positive staining for Ber-EP4 supported an origin from the basal cell layer of stratified squamous mucosa.

Koutlas et al. [39] presented a case of a 67-year old female with oral basal cell carcinoma originating on the posterior mandibular mucosa and gingiva. It presented a multifocal pattern histologically. During a 20 years follow up it recurred 20 times. Tissue samples of the tumor were evaluated with monoclonal antibody Ber-EP4 and were compared with examples of oral mucosa, skin, oral and cutaneous squamous cell carcinoma, peripheral ameloblastoma,

ameloblastoma and cutaneous basal cell carcinoma (BCC). Only neoplastic basal cells showed positive immunohistochemical staining. Additionally, microdissected neoplastic areas were evaluated for loss of heterozygosity (LOH) of the PTCH gene with markers D9S303, D9S252 and D9S287. PTCH gene mutations are reported in patients with Gorlin syndrome and sporadic cutaneous BCCs. Loss of one allele was observed with all three markers. These observations supported the inclusion of BCC in the differential diagnosis of appropriate oral mucosal neoplasms.

In [40] yet another case was reportedof intraoral BCC arising in the anterior buccal mucosa of a patient with nevoid basal cell carcinoma syndrome (NBCCS). Ber-EP4, a cell surface glycoprotein mostly expressed in BCC of the skin, has been suggested as a useful marker to support the diagnosis of oral BCC. Histopathologic and immunohistochemical features of the case were compared to examples of PA, conventional intraosseous ameloblastoma, sporadic cutaneous BCC and cutaneous BCC from NBCCS patients. Ber-EP4 expression by the oral tumor was different from both peripheral and intraosseous forms of ameloblastoma and was same to cutaneous BCC in both sporadic and syndromic settings.

5. DIAGNOSIS

Dentists and other clinicians who are familiar with the clinical manifestations of BCC are mostly able to reach the diagnosis based upon clinical examination. Histological confirmation is done by performing a skin biopsy. The clinicians experienced in the diagnosis of BCC may elect to perform the biopsy at the same time as definitive treatment (immediately prior to electrodesiccation and curettage) in cases where the clinical diagnosis of BCC are certain and the tumor lacks clinical features associated with a high risk for tumor recurrence. A few clinicians may choose to treat lesions without a biopsy if high-risk clinical features are absent. However, it is risky to decide not to perform a biopsy prior to definitive treatment as biopsy present the histological features of a tumor which gives crucial information about the aggressiveness of tumor and its chances of recurrence following treatment, as well asbiopsy eliminates the risk of misdiagnosis of a different tumor as BCC (eg. amelanotic melanoma) [41-44].

For definitive diagnosis of BCC punch biopsies, shave biopsies and excisional biopsies can be performed. Mostly simple procedures like shave and punch biopsies are performed for diagnosis, clinicians should be aware that biopsies that remove only a portion of the lesion do not always provide an accurate assessment of the histological subtype of a tumor [41-44].

Dermoscopy may also be used as a diagnostic aid in the clinical evaluation of lesions that are doubtful for BCC [45-47]. Common dermatoscopic features of BCC that are regocnized includes, “arborizing” blood vessels (discrete, thickened, red blood vessels that branch like a tree) and blue-gray ovoid nests. Pigmented BCCs usually show a brown “maple leaf” shaped blotch on dermatoscopic examination, which represent heavily pigmented aggregates of tumor cells [45].

5.1 Differential Diagnosis

The differential diagnosis varies with the subtype of BCC:

1. Early nodular variants with little ulceration clinically may be identical to benign growths such as dermal nevi, small epidermal inclusion cysts, or even sebaceous

hyperplasia. A single lesion of molluscum contagiosum has a similar appearance, as amelanotic melanoma.

2. Larger lesions with central ulceration can appear cup-shaped. These can resemble squamous cell carcinoma, keratoacanthomas, or dermal metastases from internal organs such as the colon [47].
3. Superficial BCCs may be confused with inflammatory disorders of the skin such as nummular eczema (nummular dermatitis) or psoriasis, especially when a peripheral rim of small, pearly papules is absent. In particular, the possibility of superficial BCC should be considered when a lesion presumed to be inflammatory fails to respond to topical corticosteroids. Benign lichenoid keratoses, actinic keratoses, and rarely amelanotic melanoma presenting as scaly erythematous macules may also be mistaken for superficial BCC. In general, recognition of a localized erythematous macule, patch, or thin plaque with a slightly shiny quality or peripheral pearly papules should raise suspicion for superficial BCC. When pigment is present, the differential diagnosis may include melanoma.
4. Morpheaform BCCs frequently appear similar to a scar or other site of trauma. The in duration of the lesion simulates localized scleroderma.
5. Pigmented nodular or superficial BCCs resemble melanoma or less likely a benign nevus[48].

6. CONCLUSION

Basal cell carcinoma is the most common malignant cancer of skin, frequently affecting the head and neck region; it can cause significant destruction and disfigurement by invading surrounding tissues. The dentists should always thoroughly examine the head and neck region of their patients. if they come across any nonmelanoma skin lesion in this area they should always consider bcc in the differential diagnosis. This review clearly draws attention of the valuable role of dentists in the early diagnosis and management of this cancer. It also underscores the importance of obtaining biopsy materials, careful histological examination and detection of immunohistochemical markers such as ber-ep4 which are expressed in bcc. The early diagnosis made by the dentist based on their good knowledge about the lesion and immediate referral of the patient to oral maxillofacial surgeon and oncologist for timely adequate treatment will help in reducing the morbidity rate and treatment cost, also will lead to better prognosis.

CONSENT

Not applicable.

ETHICAL APPROVAL

No human or animal subjects were used in the study and the study was approved by the ethnical research board of the institution.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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