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Original Article

Pigmented basal cell carcinoma develops De nova without pre-existing solar keratosis in skin type III and IV

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Abstract

Objective Basal cell carcinoma (BCC) is a common tumor all over the world that affects middle age and elderly people that often involve the face and scalp in people with skin type I although other skin types are inflected. Sun-damaged skin is more liable to have this disease. The objective of the study is to evaluate the different demographic and clinical pictures in a series of 140 patients with basal cell carcinoma in relation to solar keratosis and wrinkling.

Methods This is a case series descriptive study where all patients with BCC were recorded during the period from 2014-2022. All demographic features were described and a full clinical examination was carried out. Skin photo type was established for all patients according to Fitzpatrick's classification. The sites, the number of lesions, the type of lesions, the associated solar keratosis, and squamous cell carcinoma were evaluated. A histopathological examination was performed as a confirmatory test.

Results This study included 140 patients, whose ages ranged from 35-75 years with a mean of 60 years, with 95 (67.9 %) males and 45 (32.1%) females. All patients who had outdoor activities with Fitzpatrick's classification of skin type were type III and IV. The location of lesions was 117 (83.6%) on the face and scalp while in 23 (16.4%) patients, the lesions were located on the covered parts body mainly the trunk and limbs. The tumor was pigmented in 123 (87.9%) cases while in 17 (12.1%) patients lesions were non-pigmented. The associated solar keratosis was observed in 20 (14.3%) cases but no case with squamous cell carcinoma was detected. The number of lesions was multiple in 42(30%) cases while single lesions were in 98 (70%) cases. Coarse wrinkling of the face mainly the forehead and around the eyes was detected in 20 (14.3%) cases. The type of lesions were ulcerative superficial non-healing ulcers while few cases presented with nodular lesions but rarely with rolled-up rodent ulcers. Also, a few cases are presented with thread-like margins.

Conclusion Pigmented basal cell carcinoma is a common disease seen in older male patients with skin type III and IV living in highly sunny atmospheres presenting with a single pigmented superficial non-healing ulcer in non-wrinkling skin with low association with solar keratosis but no cases with squamous cell carcinoma. Accordingly, BCC develops and appears de novo without pre-existing solar keratosis.

Key words
BCC; Pigmented BCC; Solar keratosis; Wrinkling; P53.

Introduction

Basal Cell Carcinoma (BCC) is a type of skin cancer caused by non-keratinizing cells in the basal layer of the epidermis and is one of the most common forms in the world.[1] It accounts for approximately 75% of all skin cancers worldwide. In Iraq, the incidence of BCC is 53.2% of skin cancer patients.[2-4] In the United States, this disease is increasing at an annual rate

of 4-8%.[5] Increasing rates of incidence have also been reported in Europe, Canada, Asia, and Australia.[6-13] The prevalence of skin cancer in India is about 1-2%, and various studies have consistently reported SCC as being more common than BCC.[14,15] According to the Saudi Cancer Registry, nonmelanoma skin cancer (NMSC) accounts for 3.2% of all newly diagnosed cases in 2010, with BCC being more common than SCC.[16] Although BCCs can occur sporadically and with certain genodermatoses such as Gorlin's syndrome and xeroderma pigmentosa, age does not play a role in their occurrence.[17] Incidence rates double between the ages of 40 and 70.[18] There is also an increase in the incidence among those <40 years of age.[19] Males have a higher BCC rate than females (1.5-2:1).[6,20,21] Sunlight, specifically UVB rays, is responsible for most sporadic cases.[22] Based on the results of Oikarinen *et al*., BCC has increased over the past decades due to both lifestyle changes and ozone depletion in the stratosphere.[23] Lighter-skinned individuals with sun-exposed skin are more likely to develop tumors, with 20% occurring on the nose. Because BCCs are commonly found on the eyelids, the inner canthus, and behind the ear, but less common on the back of the hand and forearm, it appears that lesions are not closely correlated with areas of maximum UVR exposure. The palm, sole, and vermilion of the lips are rarely involved.[24-28] Evidence indicates that intermittent sun exposure contributes significantly to BCC risk factors (e.g., recreational tanning, occupational exposure, childhood sunburns), but chronic cumulative sun exposure does not play the same critical role as chronic cumulative sun exposure does in SCC carcinogens.[29,30] The phenotype of the skin plays an important role in mitigating the effects of UV exposure on the development of basal cell carcinoma. There is an independent risk factor for BCC associated with skin type I, which consists of fair skin, reddish or blond hair, light eye color, a tendency to freckle, light hair color, and an inability to tan.[29,30] A lower incidence rate of cancer among people of African descent can be attributed to the protective effect of skin pigmentation against carcinogenesis.[21] Smoking does not appear to increase incidence rates.[31] Alcohol consumption and BCC have been subjected to limited research, with some reports suggesting a relationship and others not.[31,32]

Genetic risk factors for BCCs include certain hereditary disorders that predispose to an early onset.[33] Gorlin syndrome (basal cell nevus syndrome) is a form of autosomal dominant genodermatosis characterized by multiple basal cell carcinomas. Its incidence ranges from 1:56,000 to 1:164,000 in the general population.[33] Xeroderma Pigmentosum and Bazex syndrome are also hereditary disorders associated with BCC. Many cancers, including BCC, exhibit dysregulation of the sonic hedgehog ligand-receptor, which encodes *PTCH1*.[33,34] Melanocortin-1 receptor (*MC1R*) polymorphisms have been linked to BCC risk. [35] Non-melanoma skin cancer (NMSC), solar keratosis, and pronounced elastosis are associated with *MC1R* variants.[36] Additionally, single nucleotide polymorphisms in the *ASIP* and *TYR* genes leading to melanin hormone regulation are associated with higher BCC risk. *TYR* gene mutations have been linked to ocular albinism, a genetic condition that increases the risk of NMSCs.[37]

Studies have shown a link between BCCs and polymorphisms in the cytochrome (*CYP*) and glutathione S-transferase (*GST*) supergene families, which are involved in metabolic and

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detoxification processes.[38] About 85% of sporadic BCCs harbor mutations in *Hh* pathway genes (*PTCH1, SMO, SUFU, TP53*). Most of these alterations are *C* to *T* substitutions at a dipyrimidine site, so-called "UV signature" mutations.[39] Between 40% and 65% of BCCs are affected by mutations in the *TP53* gene. Many cancer types, including BCC, have been linked to *P53*, whose LOH appears to be mutually exclusive with *PTCH1*.[40] *P53*, the protein encoded by *TP53*, is crucial to keratinocyte senescence, so its absence may favor BCC growth.[40] According to Sharquie *et al*. study, vitiligo has protective effects against skin cancers even though it lacks melanin. Patients with vitiligo have high levels of the P53 suppressor protein in their epidermis. The risk of skin cancer is high in people with albinism who lack melanin as well.[41] Sharquie *et al*. also proposed a Negative association between wrinkling score and the frequency of skin tumors, especially deep wrinkling. Smoking might indirectly protect against basal cell carcinoma by increasing the wrinkling score.[42,43] Several prognostic-relevant subtypes of BCC are recognized by the WHO classification, including low-risk BCCs (nodular, superficial, pigmented, fibroepithelial, adnexal differentiation/ infundibulocystic), high-risk BCCs (micronodular, infiltrating, sclerosing/ morphoeic, basosquamous, sarcomatoid), and non-prognostic BCCs (other BBCs with adnexal differentiation).). Each subtype potentially displays further histological (keratotic, nodulocystic, adenoid) and cytological variants (clear, monster, signet-ring cell).[24,44]

Nodular basal cell carcinoma, which accounts for about 50 to 80% of the total number of basal cell carcinomas, is the most common clinical subtype of basal cell carcinoma. It is most prevalent in sun-exposed areas of the head and neck. These lesions are typically shiny, pearly papules or nodules with rolled borders, arborizing telangiectasias, and smooth surfaces. The tumor can grow slowly and become large and ulcerated, a condition known as a "rodent ulcer". Invasive, advanced tumors may cause structural distortions. The histopathology reveals large malignant basaloid keratinocyte nodules with peripheral palisading (due to clefting between the tumor epithelium and the stroma), and plump spindle cells in the mucoid stroma.[25-27] Pigmented basal cell carcinoma is a sub-type of nodular BCC that exhibits increased melanization. In Iraq, BCC is a common pigmented skin condition.[4] Generally, a pigmented BCC appears in the form of a hyperpigmented, translucent papule, as well as erosion of the skin surface. The differential diagnosis includes nodular melanoma. Histologically, pigmented BCC shows similar characteristics to nodular BCC but with melanin.[4,25-27] The superficial BCC is the second most common subtype, accounting for approximately 10 to 30% of all BCCs. Typically, they appear as well-circumscribed, erythematous patches or plaques with scale, central clearing, and thin borders. They can sometimes be mistaken for inflammatory lesions or eczema without healing. It is most common to see these slow-growing lesions on the trunk, but they can also occur on the legs and, less commonly, on the head and neck.[45] Typically, superficial BCCs show multiple lobules of basaloid palisading keratinocyte tumors attached to the epidermis with lichenoid infiltrations and myxoid stroma.[46] The pigmented BCCs can sometimes occur in both nodular lesions and superficial lesions, and both can contain melanin.

Treatments for BCC include a variety of standard therapeutic modalities that are used to treat cancer including surgical excision,[47] Curettage with electrodesiccation,[48] Cryotherapy,[49] radiotherapy,[50] Moh's micrographic surgery,[51] photodynamic therapy

(PDT),[52] laser therapy,[53] intralesional interferon,[54] intralesional zinc sulphate 2%,[55] topical Imiquimod,[56] 5-fluorouracil,[56] tazarotene,[57] Topical 25% podophyllin solution,[58] and topical heat therapy.[59]

Methods

One hundred and forty patients complaining of basal cell carcinoma gathered during the period from 2014-2022 years were involved in this descriptive, observational, case-series clinical-histopathological study The study adhered to the Declaration of Helsinki. After discussing the nature of the study with all patients, informed consent forms were obtained from them. Close-up photos were taken at the same location at a fixed distance and illumination. In addition, all participating patients accepted the idea of sharing their photos. A complete history was taken and a well-established examination was conducted to establish the right diagnosis. All patients were asked their name, age, gender, place of residence, occupation, including outdoor activities, smoking, alcohol intake, and past medical and drug histories Moreover, the type, size, morphology, color, number of lesions, and lymph node examination were assessed. Lesions ranged in size from small pearly papules measuring 0.5x0.5 cm to large hyperpigmented lesions measuring 10x8 cm. The associated solar keratosis and squamous cell carcinoma were evaluated. Skin photo-type was established for all patients according to Fitzpatrick's classification,[60] facial wrinkling was classified and measured according to modified Sharquie wrinkling score (Grade I-II) as superficial, (Grade III-IV); medium, and grade (V-VI) as deep wrinkles),[42,61] an examination of the skin for signs of sun damage was conducted. The lesions were evaluated for pain, itching, and tenderness. An analysis of all demographic features was conducted. A confirmatory biopsy was carried out in all cases after a shave or incisional biopsy for histopathology assessment.

Results

One hundred and forty patients with different subtypes of basal cell carcinoma were considered in the present work, their ages ranged from 35-75 years with a mean of 60 years, with 95 (67.9 %) males and 45 (32.1%) females. All patients who had outdoor activities with Fitzpatrick's classification of skin type were type III and IV. The location of lesions was 117 (83.6%) on the face and scalp while in 23 (16.4%) patients, the lesions were located on the covered parts body mainly the trunk and limbs. Regarding the diagnosis of basal cell carcinoma, the tumor was pigmented in 123 (87.9%) cases while in 17 (12.1%) patients lesions were non-pigmented. The associated solar keratosis was observed in 20 (14.3%) cases but no case with squamous cell carcinoma was detected. The number of lesions was multiple in 42 (30%) cases while single lesions were in 98 (70%) cases. Coarse wrinkling of the face mainly the forehead and around the eyes was detected in 20 (14.3%) cases **(Figures 1-6)**. The type of lesions were ulcerative superficial non-healing ulcers while few cases presented with nodular lesions but rarely rolled-up rodent ulcers. Also, a few cases are presented with thread-like margins **(Table 1)**.

Table 1 Clinical characteristics of Basal Cell Carcinoma.

Character		*N (%)*
Location:	Face and scalp	117(83.6)
	Trunk and limbs	23 (16.4)
Color:	Pigmented	123 (87.9)
	Not pigmented	17 (12.1)
Association:	Solar keratosis	20 (14.3)
	Squamous cell carcinoma	0 (0)
The number of lesions:	Multiple	42(30)
	Single	98 (70)
Coarse wrinkling of the face:	Yes	20 (14.3)
	No	120(85.7)

Figure 1 60-year-old female with a recurrent basal cell carcinoma of the nose with no solar keratosis and no wrinkling.

Figure 2 59-year-old female patient with pigmented basal cell carcinoma but no solar keratosis.

Figure 3 60-year-old male patient with pigmented basal cell carcinoma but no wrinkling and no solar keratosis.

Figure 4 58-year-old female patient with pigmented basal cell carcinoma with thread-like margin. Also no wrinkling and no solar keratosis on the face.

Figure 5 40-year-old male with nodular non-pigmented basal cell carcinoma but no solar keratosis.

Figure 6 50-year-old male with basal cell carcinoma on the covered site of the body.

Discussion

BCCs are less frequently reported in darker-skinned individuals like Africans due to melanocyte photoprotection while reported frequently in lighter skin types for example Caucasians, Hispanics, Chinese Asians, and Japanese individuals. The commonest skin type in Iraq is type III-IV which is a dark type and less liable to skin cancer but unfortunately, still BCC is frequently seen among the general population.[42,62] In Iraq, the most common skin tumor is BCC followed by SCC, Basosquamous, keratoacanthoma, and lastly seborrheic keratosis.[42,62] In the study carried out by Sharquie *et al*. where 54 patients with various skin tumors and 108 patients as a control group were included in this study. Patients with superficial wrinkles were more commonly affected with skin tumors than those with deep wrinkles and in conclusion, confirmed a negative association between wrinkling score and the frequency of skin tumors.[42] The present study showed deep wrinkling of the face was observed in only 14.3% of BCC cases indicating that a deep wrinkle has a protective and

defensive mechanism against the development of BCC. Men were affected more frequently than females in our study, this rate supports other studies reported in the literature.[6,20] In the present study, most BCC cases are single located on exposed parts of the body like the face and scalp, these results same as prescribed in the reported studies.[24,39]

Regarding the type of lesions, the present study showed superficial BCC was the most common type, while nodular BCC is less and this result is against what was reported before in the literature as the most common subtype of BCC is nodular.[25-27] Also the study reported pigmented BCC In 87.9% of cases, this finding was similar to a previous study carried out by Sharquie *et al*.[4] These results concluded that pigmented BCC is the most common type in Iraq whether superficial or nodular types. *P53* inhibits angiogenesis, apoptosis, and genetic stability, as well as plays an anticancer role. A normal type of *P53* prevents cells with damaged DNA from entering the cell cycle.[63] In vitiligo, the incidence of skin tumors is low, especially in patients with severe generalized vitiligo.[41,64] Sharquie *et al*. reported *P53* marker is highly positive among vitiliginous patients with low frequency of skin malignancy especially BCC, this confirms the role of *P53* as protective against skin cancers.[41,65] Solar keratosis is a cutaneous neoplasm that occurs primarily on sun-exposed surfaces of the skin. Due to their fair type I skin, it is a major problem among Europeans. The problem is less common in Middle Eastern countries, such as Iraq, because of melanin photoprotection, but recent studies have shown that middle-aged and elderly people are not exempt from solar keratosis.[62,66,67] Although BCC and Solar keratosis are sun-induced tumors, the co-existence of both tumors at the same anatomical site called collision or combined tumors is extremely rarely reported in the literature and can be observed clearly in syndromes like Xeroderma pigmentosa.[68,69] Several theories exist regarding the pathogenesis of collision lesions. One theory suggests when a biphasic or biphenotypic collision occurs, it can lead to composite or intermingled lesions because a single cell type (pluripotent cell) can differentiate more than one way.[70] As another explanation, when exposed to certain carcinogenic stimuli, two adjacent neoplasms may occur simultaneously, or paracrine factors released by one neoplasm might affect vulnerable cells adjacent to it.[69,71] In the present study, combined both BCC and solar keratosis were reported in 14.3% of cases, and no squamous cell carcinoma was detected.

Conclusion

Pigmented basal cell carcinoma is a common disease seen in older male patients with skin type III and IV living in highly sunny atmospheres presenting with a single pigmented superficial non-healing ulcer in non-wrinkling skin with low association with solar keratosis but no cases with squamous cell carcinoma. Accordingly, BCC develops and appears de novo without pre-existing solar keratosis.

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