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A Clinical Study of Basal Cell Carcinoma

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ABSTRACT

Introduction: Basal cell carcinoma (BCC) is a non-melanocytic skin malignancy arising from basal cells of epidermis or follicular structures. Etiology of BCC is a multifactorial combination of genotype, phenotype, and environmental factors. There are several clinical variants of BCC including nodular, cystic, superficial, morphoeic, keratotic, pigmented and micronodular. **Aim:** The aim of our study was to analyze the recent clinical trends of basal cell carcinoma by reviewing a single institution's experience. **Methods:** Total number of 422 patients clinically diagnosed with basal cell carcinoma were included in the study. Data on age, gender, skin type, personal and family history, duration of disease, localization of lesions, clinical type of lesions, and recurrence rate were collected and analyzed. The data were statistically evaluated. **Results:** More than 80% of all BCC's were located on sun-exposed skin areas ($p<0.05$).The male /female ratio was 1:0.92. The nodular BCC was the most frequent type (59.2%), followed by the superficial (16.1%), pigmented (15.2%) and morphoeic (9.5%) types. The nodular and pigmented types were predominant located on the head and neck, whereas the trunk was the most common location for the superficial type ($p<0.05$). The tumor is commonly found in concomitance with skin lesion related to chronic sun exposure, such as actinic keratoses, solar lentigines and facial telangiectasia. During this study period, 41 cases showed recurrence of the cancer as the overall recurrence rate was 9.7%. There were no cases with metastasis or fatal outcome. **Conclusions:** The factors related to the development of BCC were older age and exposure to ultraviolet rays both in recreational and in occupational form. The prevention of BCC is based on the knowledge of risk factors, early diagnosis and treatment, particularly in susceptible populations.

Keywords: basal cell carcinoma, subtype, ultraviolet radiation.

1. INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignant neoplasm in humans and its incidence has increased over the last decades (1). The tumor usually arises from the lowermost layers of the epidermis, although a small percentage may originate from the outer root sheath of the pilosebaceous unit (2). Etiology of BCC is a multifactorial combination of genotype, phenotype, and environmental factors. Multiple risk factors have been described for BCC, but chronic exposure to ultraviolet radiation, particularly UVB is clearly the most important, progressively inducing keratinocyte carcinogenesis and resulting in BCC after several years or decades of cumulative cellular degeneration. UVB radiation generates mutagenic photoproducts in DNA, such as cyclodipyrimidine dimers, and mutations in important genes which regulate cell functions such as the p53 tumor suppressor gene (3). Apoptosis of keratinocytes after exposure to UV rays is evidence of its carcinogenic potential. UVA rays have an indirect effect by generating cytotoxic and mutagenic free radicals, favoring the effects of UVB rays. Additionally, iatrogenic or cosmetic artificial UV skin irradiation, exposure to ionizing radiation or other carcinogenic agents in the environment and immunosuppression may also increase the risk of BCC in some particular cases.

There are several clinical variants of BCC including nodular, cystic, superficial, morphoeic (sclerosing), keratotic, pigmented and micronodular (4). Each varies in terms of clinical presentation, histopathology and aggressive behavior. Nodular or cystic BCCs present as raised red, pearly, translucent lesion with peripheral telangiectasia. If untreated, the center of the tumor expands and undergoes ulceration. Pigmented BCC is equivalent to nodular variant of BCC, except for the brownish pigmentation. It should be differentiated from melanoma. Superficial tumors may present as multiple,

flat, well-defined, circumscribed, erythematous plaques with slightly raised margins. Morpheic BCC is the least common variant of BCC. This tumor presents as a subtle scar-like plaque. Nodular BCCs are the most common type, though 10-40% show a mixed pattern of two or more subtypes (5).

Despite the low mortality rates and the rare occurrence of metastases, the tumour may be locally invasive and relapse after treatment, causing significant morbidity. Local tissue destruction and disfigurement can be large, if not limited by early detection and treatment (6).

In the last few years, the interest on the study of the etiology, biology and treatment of BCC has been growing, mainly due to the world-wide increase of incidence of this disease, as well as due to the destruction of the ozone layer.

2. AIM

Therefore, the aim of our study was to analyze the recent clinical trends of basal cell carcinoma by reviewing a single institution's experience.

3. METHODS

A hospital based cross-sectional study was conducted at Department of Dermatovenerology, University Clinical Centre Sarajevo, during the 2016-2018 period. 422 patients clinically diagnosed with basal cell carcinoma were included in the study. Cases were from a mix of urban and rural environments. After informed consent, relevant history was taken and clinical examination was performed. The following factors were considered: sex, age, skin phototype according to Fitzpatrick's classification (7), personal and family history, duration of disease, localization of lesions, clinical type of lesions, and recurrence rate. Environmental factors such as exposure to ultraviolet radiation, indoor or outdoor occupation, exposure to ionic radiation and to chemical agents were also analyzed.

The anatomical sites affected by tumors were basically classified as follows: head and neck, trunk, upper extremities, and lower extremities. According to solar exposure levels, we defined three separate topographic regions of the body: a) sun-protected sites, b) intermittently sun-exposed sites, and c) permanently sun-exposed sites.

The data were statistically evaluated. Statistical significance for variables relationship was considered when $p<0.05$.

4. RESULTS

Among the 422 patients included in this study, 219 (51.9%) patients were men and 203 (48.1%) patients were women. The male /female ratio was 1:0.92. The average age of the patients with BCC was 66.4, varying from 42 to 96 years old (Table 1). There was no statistically significant difference between genders with respect to age ($p>0.05$). The BCC patients were mostly older than 50 years, with a peak age at detection of BCC of 61-70 years. There was also personal and/or family history of cancer in 41 (9.71%) of our cases.

The all of our patients were Fitzpatrick phototype II (71%) and phototype I (29%) calculated via Fitzpatrick scoring scale. The duration of BCC ranged from 1 to 120 months. The average duration of lesions from the onset to diagnosis was 18 months for both genders. The most frequent symptoms that prompted patients to look for a doctor were tumor growth, bleeding and ulceration. 66 (15.6 %) patients had multiple BCCs. The number of tumors varied between 2 and 12. Patients with multiple lesions were more likely to have a truncal tumor at first presentation.

A 303 patients (71.8%) had a positive history of solar exposure. Among these, 195 (64.3%) had had occupational exposure and 108 patients (35.7%) had had recreational exposure. There was no history of treatment with PUVA or UVB in any of the study cases. None of the patients were exposed to ionic radiation or to chemicals.

In terms of tumor location, most of the lesions were situated on the head and neck, with the face being the area most commonly affected. In 33.5% cases, the lesions were situated on the nose, while in 25.4 % cases the lesion was on the cheeks, forehead 12% and ear and preaurical area 7.1%. More than 80% of all BCC's were located on sun-exposed skin areas, revealing a statistically significant association ($p<0.05$). Of non-photoexposed skin areas, a high percentage of cases were found on the trunk 56 (13.3%); and in the sites of the body intermittently exposed to sunlight: the upper extremities (12 cases, 2.8%) and the lower extremities (11 cases, 2.6%).

The nodular pattern was present in 250 (59.2%), superficial in 68 (16.1%), pigmented in 64 (15.2%) and morpheaform in 40 (9.5%) (Table 2). Nodular tumors occurred at the mean age of 67.5 years, whereas superficial tumors were excised earlier (62.0 years). Patients with morphoeiform BCC had a mean age of 64.8 years and were predominantly women. The association between pigmentation and age, gender or anatomic site were not statistically significant ($p>0.05$).

During this study period, 41 cases showed recurrence of the cancer as the overall recurrence rate was 9.7%. There were no cases with metastasis or fatal outcome. The tumor is commonly found in concomitance with skin lesion related to chronic sun exposure, such as actinic keratoses 87 (20.6%), solar lentigines 62 (14.7%) and facial telangiectasia 44 (10.4%).

5. DISCUSSION

Basal cell carcinoma, previously known as basal cell epithelioma, is the most common cancer in humans. First described in 1824 by Jacob, it is a slow growing, locally destructive, skin tumour of the epidermis (8). The absolute incidence of BCC is difficult to determine, since non-melanoma skin cancer is usually excluded from cancer-registry statistics. However, BCC incidence is expected to increase because of aging of the population and increasing exposure to solar ultraviolet radiation due to depletion of the ozone layer (9, 10).

During the 2-year study period there was a total of 422 recorded patients with confirmed BCC. Sex ratio was almost similar with a slight male predominance. This is

different from what was found in the literature. According to the current literature, BCCs are more common in males as reported in most studies worldwide, presumably due to greater occupational and recreational exposure to UV radiation (11). Males are also associated with a greater number of tumors (12). There are, however, some studies that suggest a recent increase in the proportion of female patients. The role of tanning beds and photoexposed leisure is described as a potential risk factor (3).

The incidence of BCC increases with age. In the patients studied here the higher incidence was between 61 and 70 years of age. Elderly individuals have a less efficient immune system and have diminished DNA repair capacity what increases the risk of developing BCC (13), and are more exposed to BCC risk factors, especially due to the cumulative effect of intense and continuous sun exposure.

The incidence of non-melanoma skin cancer depends on individual susceptibility. This susceptibility is related to the amount of melanin in the skin and to the capacity of the skin to tan when exposed to ultraviolet radiation. The Fitzpatrick skin type is good predictor of relative risk of BCC among whites (14). The all of the patients in our study were classified as phototype I and II by Fitzpatrick classification. These data are similar to those found in literature which show a greater incidence in the white race (15). Darker skin is more protected against damaging effects of UV radiation from solar light mostly due to protective effect by melanin (16). None of the patients had any genetic syndrome, such as Albinism, Xeroderma pigmentosum and Nevoid Basal cell carcinoma syndrome, which present a higher risk of incidence of BCC.

Chronic sun exposure is one of the most important risk factors for the development of BCC. BCCs typically have a delay of diagnosis of about 15 to 20 years between the time of UV damage and clinical onset (17). The mechanism of BCC formation via UV radiation is by direct DNA damage, indirect DNA damage through reactive oxygen species, and immune suppression (14). UVB irradiation directly damages cellular DNA and RNA causing covalent bonding between adjacent pyrimidines, and formation of mutagenic products. UVA produces the formation of toxic reactive oxygen species. UV exposure also causes dose-dependent suppression of the cutaneous immune system, harming the local antitumor monitoring activity of dedritic cells (18). In the present analysis, we found increasing BCC risk to be associated with UV exposure in both women and men.

BCC characteristically arises in body areas exposed to the sun and is most common on the head and neck, followed by the trunk and arms and legs. BCC have also been reported in unusual sites, including the axillae, breasts, perianal area, genitalia, palms and soles (10). In the current study, face was the most common affected sites in both males and females. This reflects the importance of solar radiation as the main causative factor in the pathogenesis of this condition. Facial BCC mainly affected the centrofacial sites, namely, nose, cheeks, and eyelid skin. Other sun-covered skin areas were much less commonly involved. Other studies have also demonstrated similar distribution of BCC (19-21).

Nodular BCC is the classic form, accounting for 50 to 79% of all BCCs (22). Lesions consist of papules or nodules with a pearly, shiny quality and small arborizing telangiectasias. The most common sites for nodular BCCs are the face, especially the nose, cheeks, forehead, nasolabial folds, and eyelids. Patients often give a history of crusting and recurrent bleeding. Ulceration is frequent, and term "rodent ulcus" refers to these ulcerated nodular BCCs. As the results of our study nodular BCC was the most occurring type 250 (59.2%). Epidermal ulceration was observed in most patients 180 (72%).

Superficial BCC is the second most common clinical subtype. A lesions typically appears as well circumscribed, scaly, pink to red macule, patch or thin plaque. They have a predilection for the shoulders, chest, or back, and multiple lesions may be present. There are also pigmented variants of superficial BCC. Portions of superficial BCCs can evolve into nodular BCC over time. In our study, superficial BCC occur predominantly on the trunk. Because the trunk is not continuously exposed to sunlight, intermittent sun exposure may be especially important in the etiology of superficial BCC (22). At the time of diagnosis, 68 (16.1%) patients had superficial BCC.

Morpheaform or sclerosing BCCs constitute 5 to 10% of BCCs. It is called sclerosing due its clinical resemblance to an indurated plaque of localized scleroderma. Lesions present as pink to ivory-white, smooth, scar-like, indurated plaques or depressions with ill-defined borders. The biologic behavior is usually more aggressive, with extensive local destruction. In our study, morpheaform BCC was seen in 40 (9.5%) cases.

BCC often appears as an isolated lesion. Multiple BCCs is possibly linked to a number of risk factors including genetic factors, an age more than 60 years at the first presentation, male sex, skin phototype (I and II), intermittent sun exposure and sunburns, history of radiotherapy, larger tumor size, truncal tumor, and geography of area especially high latitude (23, 24). In our study, 66 (15.6%) cases had more than one BCC. Our data show that patients with a truncal tumor at first presentation are at increased risk of having more than one lesion.

Patients with multiple BCC are prone to both recurrence of previous tumor and development of new BCCs. The literature is quite variable in relation to the recurrence rates of BCCs, reporting rates between 10% and 67% (25). This occurs more commonly in multifocal superficial and sclerodermiform tumors (26). The latency period between surgery and recurrence may vary from two months to two years, frequently occurring in the first six months. During this study period, 41 cases showed recurrence of the cancer as the overall recurrence rate was 9.7%.

The most common predictor of BCC development is a history of squamous cell carcinoma or BCC. Patients are at least ten times more likely to develop a second BCC if they have a BCC history compared to patients without a history of non-melanoma skin cancer (27). New skin

cancers tended to be of the same cell type as the previous skin cancers. For BCC, risk was higher among patients who were male, were over the age of 60 years, had more prior skin cancer, had severe actinic damage, or who burned easily with sun exposure (28). Because these patients have higher risk of developing a second primary BCC, the prevention should include long-term follow up for all patients with a history of BCC.

Though there are no premalignant skin lesions identified for BCC, the presence of actinic keratosis in the clinical exam is an indicator that the individual has been exposed to a significant quantity of ultraviolet B rays (29, 30). In the present study, 87 patients (20.6%) presented actinic keratosis in the physical exam, showing skin damage caused by the sun.

Metastasis in BCC is rare and the incidence varies between 0.00285 and 0.1% (31). Risk factors for metastasis are similar to those for recurrence. No case of metastasis or death occurred in the patients surveyed in the present study.

6. CONCLUSIONS

BCC is a very complex disease, with many factors influencing its development. In our study, the factors related to the development of BCC were: older age and exposure to UV rays both in recreational and in occupational form. The high number of BCC diagnosed on sun-exposed skin, and particularly on the face, corroborates the widely accepted association between these neoplasm, and long term UV-radiation

The high frequency of BCC, and the progressive increase in its incidence make it an environmental and occupational disease, with a clear impact on the patients' quality of life. This cases a significant burden to the health system, especially in cases of invasive behavior and relapse after treatment (32). The education of patients regarding risk factors and attention to the diagnosis of minor lesions by self-examination are essential in prevention and improved prognosis, particularly in susceptible populations.

The evaluation of the epidemiologic characteristics of BCC is crucial for enhancing the effect of mass information campaigns and managing the available resources in Dermatology Departments, in order to control the increasing neoplasm numbers and promptly offer effective diagnostic and therapeutic procedures to an increasing oncologic population.

- **Declaration of patient consent**: The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution**: Each author gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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