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VARIATIONS IN CLINICAL PRESENTATION OF BASAL CELL CARCINOMA

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SUMMARY – Basal cell carcinoma (basalioma, BCC) is the most common skin cancer and the most common human malignancy in general, with a continuously increasing incidence. In most cases, BCC develops on chronically sun-exposed skin in elderly people, most commonly in the head and neck region. Besides chronic UV radiation, other risk factors for the development of BCC include sun bed use, family history of skin cancer, skin type 1 and 2, a tendency to freckle in childhood, immunosuppression, previous radiotherapy, and chronic exposure to certain toxic substances such as inorganic arsenic. There are numerous variations in clinical presentation of BCC, such as nodular BCC, ulcerating BCC, pigmented BCC, sclerosing BCC, superficial BCC, and fibroepithelioma of Pinkus. Each varies in terms of clinical presentation, histopathology and aggressive behavior. Treatment modalities for BCC include surgical excision, cryosurgery, curettage, electrodessication, radiotherapy, photodynamic therapy, topical cytostatics, and immunomodulators. If left untreated or inadequately treated, BCC may become invasive and locally destructive, although it very rarely metastasizes. Due to the extremely high incidence of BCC, medical professionals should be familiar with its manifold clinical presentations.

Key words: *Carcinoma, basal cell – etiology; Carcinoma, basal cell – diagnosis; Skin neoplasms – etiology; Skin neoplasms – pathology; Skin neoplasms – diagnosis*

Introduction

Basal cell carcinoma (BCC) is undoubtedly the most common malignant cancer in fair-skinned adults. It is a relatively slowly expanding, painless, locally aggressive, and recurrent malignant epidermal neoplasm. BCC arises from undifferentiated cells in the basal cell layers of the lower epidermis or from outer root sheet of the hair follicle[1-3]. Recent studies have shown that two-thirds of the tumors are located in the head and neck region. The incidence of BCC worldwide has increased substantially over the past several decades and shows geographical variation[4,5]. Several epidemiological studies have clearly demonstrated that the incidence of BCC is lower in more polar latitudes than in equatorial latitudes. BCC may occur at any age, but is more common after the age of 60. According to gender, BCC is more common in men than in women[1]. It has been shown that patients with BCC have an increased risk of developing further BCC[5].

Clinically, this tumor usually presents as a slowly growing, flesh-colored, well-defined papule or nodule with telangiectasias located on the upper two-thirds of the face, above the line connecting the angle of the mouth and earlobe. However, according to clinical appearance, histopathologic analysis, and aggressiveness there are several variants including nodular, ulcerated, pigmented, sclerosing, cystic, superficial, fibroepithelioma, metatypical BCC, and basal cell nevus syndrome (Gorlin-Goltz syndrome)[1-3].

Although rarely metastatic, its malignant nature is sometimes emphasized by the local tissue destruction, disfigurement, and even death if left untreated[4].

Etiology and Pathogenesis

Various endogenous and exogenous factors, or a combination of both may be responsible for the develop-

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ment of BCC. BCC may, rarely though, be inherited in an autosomal dominant pattern due to mutation in the gene located on chromosome 9q22.3-q31. The majority of BCCs are acquired and predominantly located in the skin areas at chronic sun exposure. It has been known for many years that there is a strong positive correlation between BCC and decades of sun exposure. Thus, recent epidemiologic studies have demonstrated a higher incidence of BCC in more equatorial latitudes than in polar latitudes. Ultraviolet B (UVB) radiation (sunburn spectrum of 290 to 320 nm) is considered to be an important factor for the induction of tumors. UVB radiation damages DNA and its repair system, and alters the immune system resulting in progressive genetic alterations and formation of neoplasms. Other risk factors include sun bed use, family history of skin cancer, skin types 1 and 2, a tendency to freckle in childhood, immunosuppression, and Irish, Scottish, Scandinavian, or German heritage[7,8].

BCC may also occur at the skin site that has previously been treated with radiotherapy, or at the site of previous trauma such as scars, burns, and beneath prostheses. The etiology of BCC in some cases might be associated with chronic systemic exposure to certain toxic substances such as inorganic arsenic[1].

Clinical Features

BCC can take on many clinical appearances. There are several clinical variants of BCC including nodular, ulcerated, pigmented, superficial, sclerosing, cystic, fibroepithelioma, and basal cell nevus syndrome (Gorlin-Goltz syndrome)[1,9]. Each varies in terms of clinical presentation, histopathology and aggressive behavior.

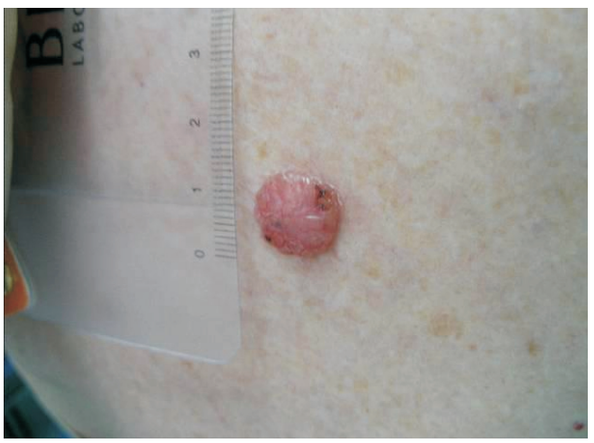

Fig. 1. Nodular basal cell carcinoma.

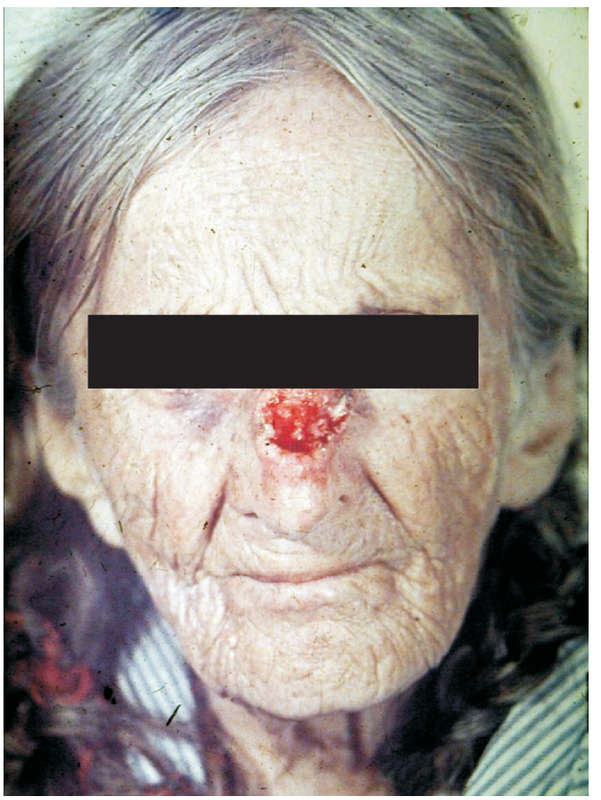

Fig. 2. Ulcerating basal cell carcinoma.

Nodular BCC is the most common variant, which is a slowly expanding, painless, flesh-colored, translucent, firm, well-defined papule or nodule with pearly appearance and telangiectasias (Fig. 1). The tumor occurs predominantly in sun-exposed skin, including the face, scalp, ears, neck, and less often shoulders, upper back

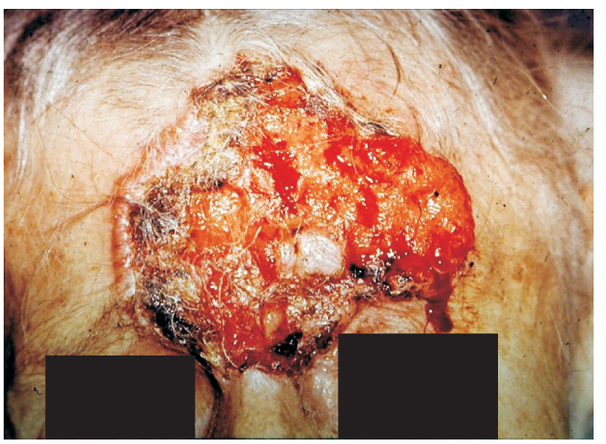

Fig. 3. Rodent ulcer.

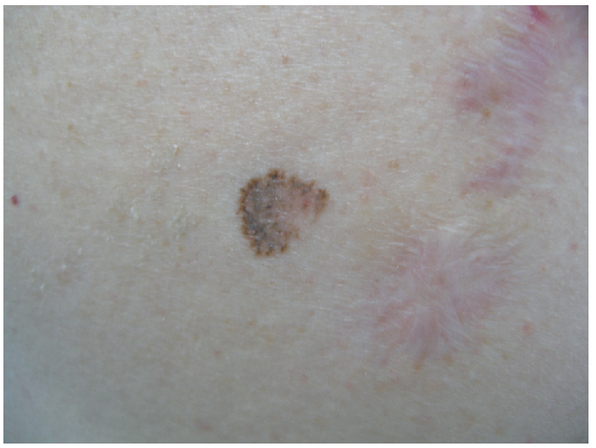

Fig. 4. Pigmented basal cell carcinoma.

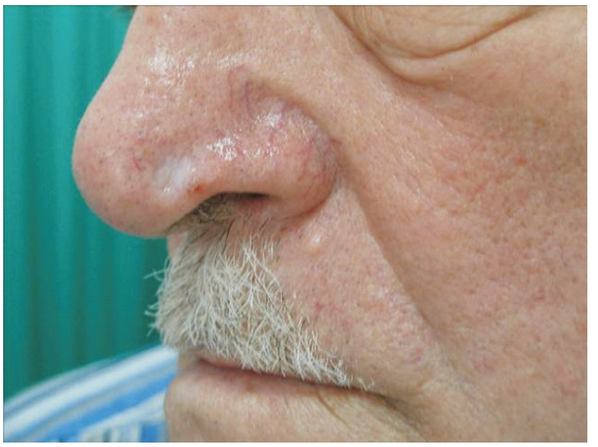

Fig. 6. Sclerosing basal cell carcinoma.

and chest. The growth pattern is irregular, forming a multi-lobulated surface. The lesions vary in size from a few millimeters to centimeters in diameter. The most common presenting complaint is bleeding or scabbing sore that heals and recurs. If untreated, the center of the tumor expands and undergoes ulceration. In general, nodular BCC has a favorable prognosis.

Ulcerating BCC comprises ulcus rodens and ulcus terebrans characterized by the appearance of painless, large papulonodular lesion with central ulceration, and rolled border[6,7,10]. Spontaneous bleeding may occur. Whereas the rodent ulcer shows a horizontally oriented spread, ulcus terebrans shows more vertically oriented spread causing significant destruction of the skin and underlying cartilage and bone (Figs. 2 and 3). Life-threatening complications such as meningitis or massive hemorrhage caused by erosion of blood vessels may occur. Despite the extension of these lesions, BCC rarely metastasizes, but when it does, the patient usually has an extremely extended and ulcerated lesion (e.g., >10 cm) that has been present for many years[3,7,11].

Pigmented BCC is equivalent to nodular variant of BCC, except for the brownish pigmentation. A blue-purple, dermal nodule is typical of this uncommon variant of BCC (Fig. 4). The cyst is formed by necrosis and degeneration of the center of a nodular BCC[7].

In contrast to other types of BCC, ***superficial BCC*** is the least aggressive form of BCC usually occurring on the trunk and extremities. The superficial BCC may present as multiple, flat, well-defined, circumscribed, erythematous plaques with slightly raised margins (Fig. 5).

Sclerosing (synonym morpheic or desmoplastic) BCC is the least common variant of BCC. This tumor

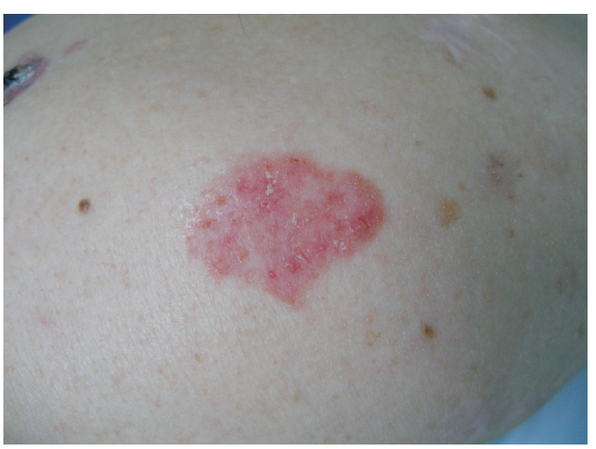

Fig. 5. Superficial basal cell carcinoma.

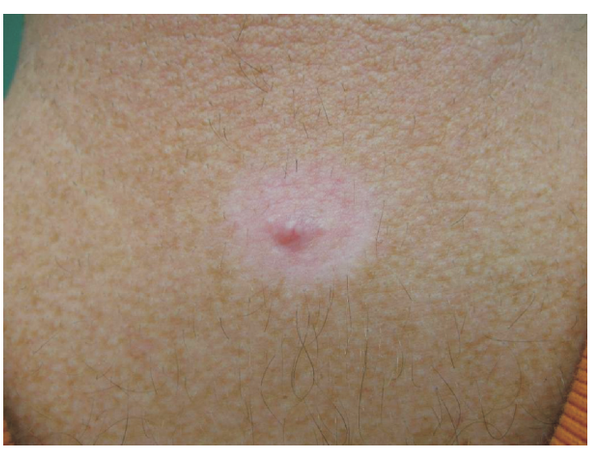

Fig. 7. Fibroepithelioma of Pinkus.

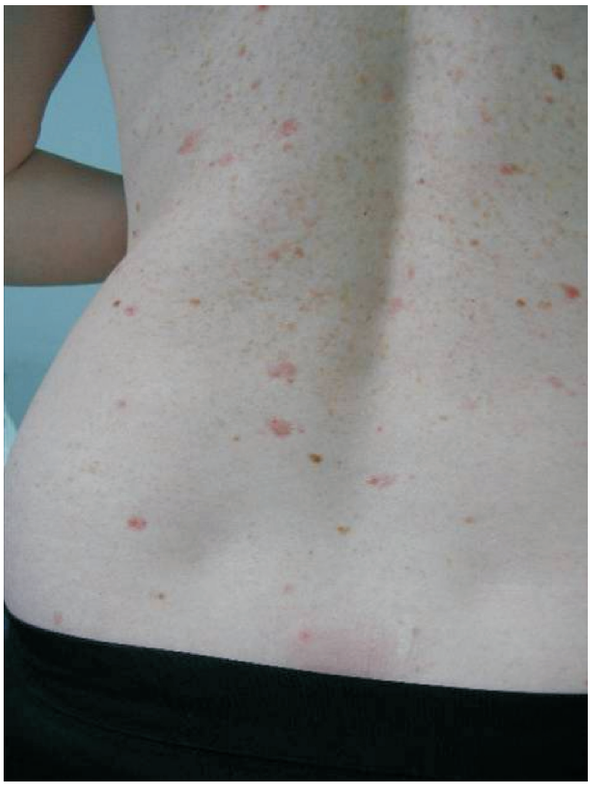

Fig. 8. Gorlin-Goltz syndrome.

is a firm, flat to slightly raised, pale-white to yellow lesion that may resemble scar tissue clinically (Fig. 6). It is usually localized on the face, especially around the nose or on the forehead or cheeks. It is waxy on palpation, recurrent, with ill-defined border, without ulceration, locally aggressive. It is also the most difficult to eradicate.

Fibroepithelioma of Pinkus is a rare variant of BCC which clinically presents as a single or multiple well-defined red plaques with adherent scaling and flesh-colored nodule without ulceration on the trunk, inguinal and crural areas (Fig. 7)[1,3,6].

Gorlin-Goltz syndrome is characterized by the presence of multiple BCCs, palmoplantar pits and odontogenic keratocysts associated with abnormalities involving the central nervous system, skeletal system, and eyes (Fig. 8)[12]. It is inherited in an autosomal dominant pattern, with high penetrance and variable expressivity of the gene located on chromosome 9q22.3-q31.

When examining patient's skin, one should always check scars and previously irradiated or traumatized skin surfaces, as BCC can develop in such localizations too

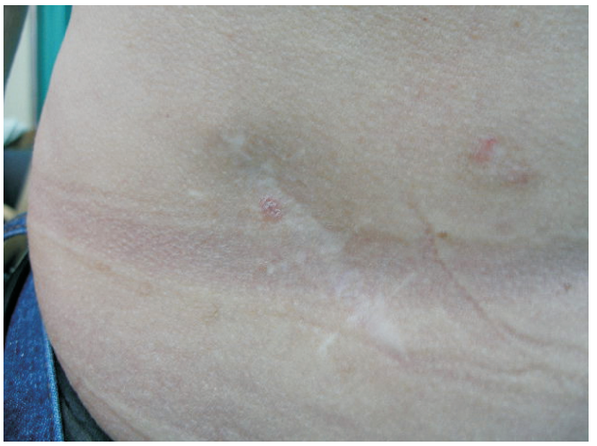

Fig. 9. Basal cell carcinoma arising in a previously traumatized skin area.

(Fig. 9). Even though clinical recognition of BCC usually does not represent difficulty for experienced dermatologist, sometimes dermatoscopic examination can clarify the diagnosis. The most significant dermoscopic features of BCC are scattered vascular pattern, micro-arborizing, telangiectatic or atypical vessels, milky-pink background and brown dots/globules (Fig. 10)[13]. However, histopathologic analysis is crucial for confirmation of the diagnosis. Histologically, BCC is composed of basaloid monomorphous epithelial cells with characteristic peripheral palisading of the hyperchromatic nuclei and the formation of pseudovascular spaces around the tumor nests[6,14].

Differential Diagnosis

BCCs may resemble squamous cell carcinoma, keratoacanthoma, actinic keratosis, or molluscum contagio-

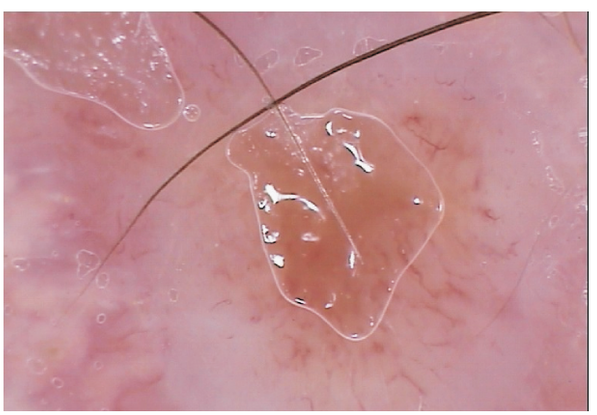

Fig. 10. Basal cell carcinoma dermatoscopy.

sum[8]. It may be clinically impossible to distinguish a flesh-colored intradermal nevus from a BCC. BCCs show varying pigmentation irrespective of their behavior. Pigmented BCC may mimic pigmented seborrheic keratosis, nevi, angiokeratoma, superficial spreading or nodular malignant melanoma. Sclerosing BCC can easily be overlooked due to its resemblance to a scar. Superficial BCC is often misdiagnosed as psoriasis or the nummular type of eczema, but lesions lack the silvery scale of psoriasis and, on contrary to eczema, BCC has sharp border. An ulcer on the lower extremities may represent a BCC or squamous cell carcinoma. According to some authors, it takes several years to recognize this skin tumor and make appropriate diagnosis in these patients[7,10]. In addition, fibroepithelioma of Pinkus may sometimes mimic amelanotic melanoma.

Treatment

Different treatment modalities for BCC include surgical excision, cryosurgery, curettage and cautery, electrodessication, radiotherapy, photodynamic therapy, topical cytostatics, and immunomodulators. The treatment of BCC is determined by the size and location of the tumor, clinical variant, patient age and comorbidities such as diabetes mellitus and hypertension. Surgical excision is the most common treatment of BCC and therapy of choice for well-defined nodular BCC, pigmented BCC, metatypical BCC and fibroepithelioma of Pinkus. The main advantage of surgical excision in comparison to other treatment modalities is that excision allows for confirmation of surgical margins and may result in more acceptable scar than the one caused by electrosurgery. Electrosurgery, cryosurgery and topical cytotoxic agents such as 5-fluorouracil are often used in cases of superficial BCC, but recurrences are very common.

Sclerosing BCC is the most difficult variant to eradicate. Therapy of choice for sclerosing BCC is microscopically controlled surgery or Mohs' surgery. This method is also used for recurrent, large BCCs, and for tumors in anatomical areas difficult to treat such as the eyes, nose and ears. Topical immunomodulator (imiquimod 5% cream) is shown to be 85% effective for superficial BCC on the trunk and extremities[5,10].

Radiotherapy is useful for small-sized (less than 2 cm) nodular BCC on the face, or when major surgery is contraindicated.

According to some authors, photodynamic therapy is shown to be 87% effective for superficial BCC[5].

All patients with BCC require follow up, regardless of the treatment used, as approximately 40% will develop a second BCC or recurrence at the treated site within 5 years[7,10]. Recurrent tumors generally have poorer cure rates with most treatment modalities compared with the treatment of primary tumors[5].

It is important to emphasize that BCC should not be removed by any method which would not allow for histopathologic analysis in any patient with personal and/or family history of dysplastic nevi or melanoma[15].

Conclusion

As BCC is the most common skin cancer and human malignancy in general, with a trend of continuing rise in its incidence, timely recognition by medical professionals is extremely important. Therefore, the awareness of many variations in clinical presentation of BCC, as well as the understanding of its behavior is an imperative for early diagnosis and appropriate treatment and future prognosis of this tumor.

References

1. BRAUN-FALCO O, PLEWIG G, WOLFF HH, BURGDORF WHC. Basal cell carcinoma. In: BRAUN-FALCO O, PLEWIG G, WOLFF HH, BURGDORF WHC, eds. Dermatology. 2nd ed. Berlin: Springer-Verlag, 2000:1475-83.
2. NGUYEN AV, WHITAKER DC, FRODEL J. Differentiation of basal cell carcinoma. Otolaryngol Clin North Am 1993;26:37-56.
3. BURG G. Atlas of cancer of the skin. 1st ed. Philadelphia: Churchill Livingstone, 2000:14-9.
4. ROEWERT-HUBER J, LANGE-ASSCHENFELDT B, STOCKFLETH E, KERL H. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol 2007;157 (Suppl 2):47-51.
5. WONG CSM, STRANGE RC, LEAR JT. Basal cell carcinoma. BMJ 2003;327:794-8.
6. du VIVIER A. Basal cell carcinoma. In: du VIVIERA., eds. Atlas of clinical dermatology. 3rd ed. Edinburgh: Churchill Livingstone, 2002:184-93.
7. WHITE G. Non-melanoma skin cancer. In: WHITE G, eds. Color atlas of dermatology. 3rd ed. Philadelphia: Elsevier Limited, 2004:319-23.
8. MILTON JS. Common cutaneous malignancies. In: FITZPATRICK JE, AELING JL, eds. Dermatology in secrets in color. 2nd ed. Philadelphia: Hanley & Belfast, 2001:313-4.
9. LEAR W, DAHLKE E, MURRAY CA. Basal cell carcinoma: review of epidemiology, pathogenesis, and associated risk factors. J Cutan Med Surg 2007;11:19-30.
10. HABIF TP. Premalignant and malignant non-melanoma skin tumors. In: HABIH TP., eds. Skin disease diagnosis and treatment. 2nd ed. Philadelphia: Elsevier Inc., 2005:424-31.

11. BORK K, BRÄUNINGER W. Basal cell carcinoma. In: BORK, BRÄUNINGER W, eds. Skin diseases in clinical practice. 2nd ed. Philadelphia: WB Saunders Company, 1998; 227.
12. AHMED N, SALMAN M, MANSOOR MA. Gorlin-Goltz syndrome. J Coll Physicians Surg Pak 2007;17:568-9.
13. JOHR R, SOYER HP, ARGENZIANO G, HOFMANN-WELLENHOF R, SCALVENZI M. Non-melanocytic lesions. In: FALE UREDNICI. Dermoscopy: the essentials. 2nd ed. London, Elsevier Limited, 2004:216-7.
14. STEVENS A, LOWE JS, YOUNG B. Skin. In: JOHR R, SOYER HP, ARGENZIANO G, HOFMANN-WELLENHOF R, SCALVENZI M, eds. Basic histopathology. 4th ed. Edinburgh: Churchill Livingstone, 2002:249.
15. KHATRI KA. Ablation of cutaneous lesions using an erbium: YAG laser. J Cosmetic Laser Ther 2003;5:1-4.

Sažetak

RAZNOLIKOSTI KLINIČKE SLIKE BAZOCELULARNOG KARCINOMA

M. Buljan, V. Bulat, M. Šitum, L. Lugović-Mihić i *S. Stanić Duktaj*

Bazocelularni karcinom (bazaliom, BCC) je najčešći zloćudni tumor kože i najčešći zloćudni tumor u ljudi, a njegova učestalost u stalnom je porastu. U većini slučajeva BCC nastaje na kronično osunčanoj koži u odraslih osoba, najčešće u području glave i vrata. Uz kronično izlaganje UV zrakama u rizične čimbenike za nastanak BCC spadaju uporaba solarija, pozitivna obiteljska anamneza tumora kože, tip kože I i II, sklonost nastanku pjegavosti u djetinjstvu, imunosupresija, prethodna radioterapija i kronična izloženost toksičnim noksama poput anorganskog arsena. Postoje brojne raznolikosti kliničke slike BCC. Klinički oblici BCC uključuju: nodularni BCC, ulcerozni BCC, pigmentirani BCC, sklerozirajući BCC, superficijalni BCC i Pinkusov fibroepiteliom. Uz raznoliko kliničko očitovanje navedeni oblici BCC razlikuju se u histološkoj slici te po stupnju lokalne agresivnosti. Metode liječenja BCC uključuju: kirurško odstranjenje novotvorine u cijelosti uz patohistološku analizu, krioterapiju, kiretažu i elektrodisekciju, radioterapiju, fotodinamsku terapiju, te lokalnu primjenu citostatika i imunomodulatora. Neliječen ili neodgovarajuće liječen BCC može postati invazivan i lokalno agresivan, iako vrlo rijetko metastazira. S obzirom na vrlo visoku učestalost BCC liječnici bi trebali poznavati mnogobrojne raznolikosti u kliničkom očitovanju ovog tumora kako bi se dijagnoza postavila u ranoj fazi kada su i mogućnosti liječenja veće, a prognoza bolja.

Ključne riječi*: Karcinom, bazocelularni – etiologija; Karcinom, bazocelularni – dijagnostika; Kožne neoplazme – etiologija; Kožne neoplazme – patologija; Kožne neoplazme – dijagnostika*