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Basal cell carcinoma: a frequent challenge

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Abstract

Basal cell carcinoma is a slow-growing, malignant epidermal tumor predominantly affecting sun exposed areas in Caucasians, accounting for up to 80% of all diagnosed skin cancers, with a rising incidence. Chronic UV radiation, in association with constitutional factors, plays the main role in its etiology. Inappropriate activation of the hedgehog signaling pathway seems to be a key pathogenesis mechanism. Basal cell carcinoma metastases are extremely rare, but it is a locally invasive tumor that can cause significant destruction of the surrounding tissues, with their functional and esthetic impairment. There are four main clinical types of basal cell carcinoma, although clinical classification is of poor prognostic significance. Preselection of suspicious lesions and treatment planning include noninvasive diagnostic techniques: dermoscopy, confocal microscopy and ultrasoud imaging, yet histopathology remains the "gold standard" of basal cell carcinoma diagnosis. In terms of the histological growth pattern, which is essential for the prognosis, basal cell carcinoma may be divided into circumscribed or diffuse types. Surgical excision is considered to be a first line treatment option, but there are numerous less invasive treatment modalities for low-risk basal cell carcinoma. Prevention strategies are focused on behavioral modifications, regular follow up and use of chemopreventive agents in high-risk patients.

Key words

Carcinoma, Basal Cell + diagnosis + classification + therapy + surgery; Risk Factors; Combined Modality Therapy; Neoplasm Recurrence, Local; Diagnosis; Treatment Outcome

Basal cell carcinoma (BCC) is a slow-growing, malignant epidermal tumor predominantly affecting sun exposed areas in Caucasians. Jacobs was the first to describe the lesion called »rodent ulcer« in 1827, and in 1900 Krompecher first identified it as an epithelial carcinoma, after histopathological examination (1, 2).

Epidemiology and risk factors

Basal cell carcinoma is the most frequent skin malignancy, accounting for up to 80% of all diagnosed skin cancers, and its incidence keeps rising. Older patients, after the 5th decade of life, are mainly affected, although endogenous and lifestyle factors may contribute to BCC appearance in younger population.

Great Britain annually registers about 30000 new cases of BCC, but it is estimated that the real incidence is even higher, because the notification system registers patients, instead of the number of lesions; also some patients are treated by non-surgical methods, without histopathological confirmation and registration. Bath Hextall et al. analyzed the period between 1996 and 2003, and reported an average annual BCC incidence growth of 3%, with a relative maximum in the population aged 30-39 years (3). In the same study, female patiens were more frequently affected if younger than 50 years of age, while males were predominant if older than 55 years. Yet another conclusion was that the younger the patient, the more aggressive BCC appered, as well as a higher relative risk of developing another BCC (3). The

incidence of BCC in USA reaches over 1200000 new cases annually, while the maximum incidence was reported in Australia - over 730 new cases per 100000 inhabitants per year (4). According to the Cancer Registry of Vojvodina, in a 5-year period (2004-2008), in this Serbian province there was a total of 2764 cases of BCCs 553 per year on average, with an incidence rate of 27.44 new cases per 100000 inhabitants, while females were slightly predominant 1.15 : 1 (5). However, this incidence is probably higher, since reporting a BCC is not obligatory in our health system.

Risk factors for developing basal cell carcinoma include chronic exposure to UV radiation, skin phototypes I and II, immunosupression, specific genodermatoses related to instability of epidermal genome leading to oncogenic transformation (Gorlin-Goltz syndrome, Bazex syndrome, xeroderma pigmentosum, Rombo syndrome, albinism), and chronic exposure to arsenic and coal-tar derivatives. Risk factors related to locoregional recurrence are X-ray radiation sites, chronic inflammation (scars, draining sinuses, ulcerations, burns), and certain preexisting benign tumors and dermatoses (sebaceous nevi, desmoplastic trichilemmoma, neurofibroma, pilomatricoma, porokeratosis, viral warts) (1, 2, 6).

Pathogenesis and biologic behavior

Ultraviolet (UV) radiation induces structural changes in epidermal DNA, and such damages are usually repaired. Insufficient cellular repair mechanisms may contribute to preservation and replication of induced mutations, and to malignant alterations of the involved tissue. Mutations lead to inappropriate activation of the hedgehog (HH) signaling pathway which is an early event in tumor formation (6). Genetic research of BCC cells showed that mutations of the tumor suppressor gene p53 are connected to aggressive biologic behavior, mutations of the gene Bcl-2 that encodes production of apoptosis inhibiting protein are usually found in indolent BCCs, and mutations of the tumor suppressor PTCH gene are usually found in nevoid BCC syndrome. Besides mutagenicity, UV radiation induces local immunosupression by reducing the number of Langerhans cells and by stimulating epidermal supressor T lymphocytes (1, 2). BCC cells produce type I and IV collagenase, which are responsible for invasiveness of the tumor (1). Biologic behaviour of BCC cells strongly depends on their interaction with the stroma, for example aggressive growth is associated with extensive stromal fibroplasia, which reduces success of all applied therapeutic options (2).

BCC metastases are extremely rare, and their estimated frequency ranges from 0.0028% to 0.5%. Diagnostic criteria for BCC metastasis were defined by Lattes and Kessler in 1951.: they have a distant location without evidence of direct extension binding it to the primary tumor, while primary and metastatic tumors must show a similar histological pattern. So far, about 240 cases of metastatic BCCs have been reported in literature, and the following conclusions were drawn: metastases are twice more frequent in male patients than in female patients; they tend to spread by lymph and blood systems; survival rate is as low as 50% of patients eight months following the diagnosis; in 2/3 of cases the primary tumor is located on the face; diameter and the depth of the tumor both affect the tendency to spread (7, 8, 9). Low metastatic potential of BCC cells may be due to their stromal dependance, e.g., experimentaly transplanted tumors do not survive without the adjacent dermal tissue (1, 9).

Nevertheless, BCC is a locally invasive tumor that can cause significant destruction of the surrounding tissues, causing functional and esthetic impairment. It spreads towards the least resistant tissues, so instead of invading the bone, cartilage or the muscle, tumor cells invade along the periosteum, perichondrium, perineurium or the fascias. Basal cell carcinoma is mainly unicentric, which means that multiple microscopic extensions of the tumor produce multiple closely positioned skin lesions (1).

Clinical features

Approximately 85% of basal cell carcinomas develop in the head and neck region, usually on the nose, cheeks, periorbital region, scalp and periauricular area, respectively. Rare locations are hands, lower lip and penis (1,10). BCCs frequently reccur when located in the inner canthus, base of the nose, preauricular and postauricular areas (along the embryonic fusion planes) (1). BCC is usually asymptomatic, while pain is described in some aggressive histologic forms as a result of perineural infiltration (2).

There are four main clinical types of BCC, but clinical classification is of little or no importance for the prognosis:

1. Nodular BCC is a pinkish or flesh colored papule, translucent, often with visible telangiectasias, with pearly borders (Figure 1a) and a tendency to ulcerate and bleed (Figure 1b). Differential diagnosis includes: fibrous papule, sebaceous hyperplasia, dermal nevus, seborrheic keratosis, adnexal tumors (mostly trichoepitheliomas), amelanotic melanoma;

2. Pigmented BCC is a sub-type of nodular BCC which exhibits bluish to brownish color (Figure 2), resembles a melanoma, pigmented seborrheic keratosis, angiokeratoma or traumatized nevus;

3. Superficial BCC is an erythemosquamous patch (Figure 1c) which should be differentiated from eczema, psoriasis, dermatophytosis, actinic keratosis, Bowen's disease and extramammary Paget's disease. In 2010, Popadić et al. reported a patient with penile superficial BCC (10). Although such occurrence is extremely rare, it is important to know that BCC may affect areas seldom exposed to sunlight;

4. Morpheaform BCC appears like a scar or circumscribed scleroderma (Figure 1d).

The prognosis of basal cell carcinoma is closely related to its size. Giant BCC is defined as a tumor larger than 5 cm in diameter, that generally has the worst prognosis (2).

A rare distinct clinical entity is a nevoid basal cell carcinoma syndrome, also known as Gorlin-Goltz syndrome**,** an autosomal dominant hereditary disorder caused by a mutation of tumor suppressor PTCH gene. The prevalence is variable, from 1:56000 in UK, and 1:256.000 in Italian population, to 1:13 million in Korea. Main skin manifestations include multiple BCCs, benign dermal cysts and palmoplantar pits. It involves other organ systems such as jaws (odontogenic keratocysts), skeletion (rib, vertebral and skull abnormalities), ocular, auditory, cardiovascular, genitourinary, respiratory, gastrointestinal and the central nervous system. The main cause of early mortality in 5-10% of patients is medulloblastoma. Diagnostic criteria were defined by Evans et al. in 1993, and modified by Kimonis et al. in 1997 (11).

Noninvansive diagnosis of basal cell carcinoma

Naked-eye skin examination is often insufficiently sensitive, so clinical preselection of suspicious BCC lesions and treatment planning relies upon noninvasive diagnostic techniques: dermoscopy, confocal microscopy and ultrasoud imaging.

Dermoscopy is widely used owing to its simplicity and affordable equipment. Hend-held dermoscopes allow optical magnification of 10x,

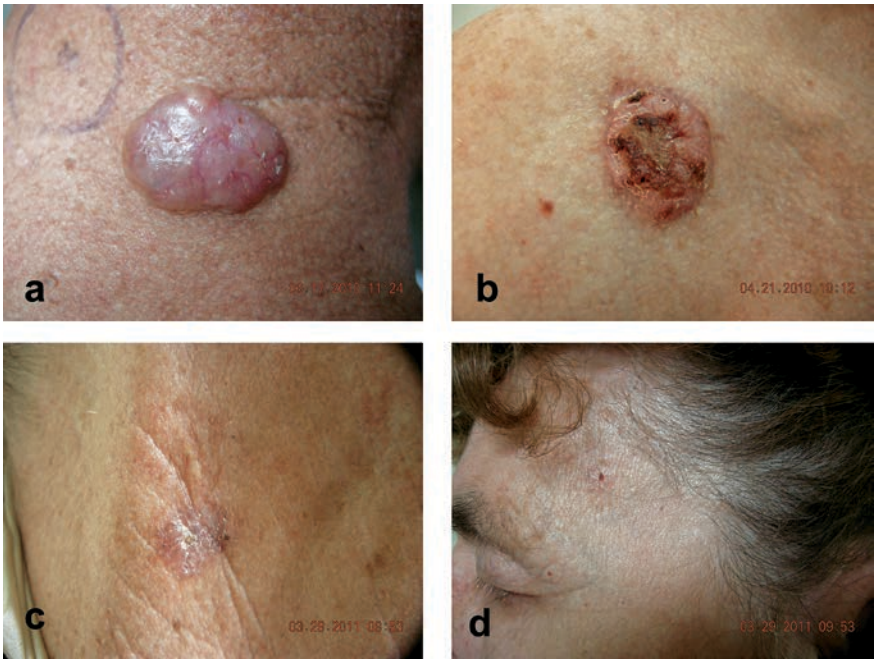

Figure 1. Main clinical types of BCC: a) nodular; b) nodular ulcerated; c) superficial; d) morpheaform

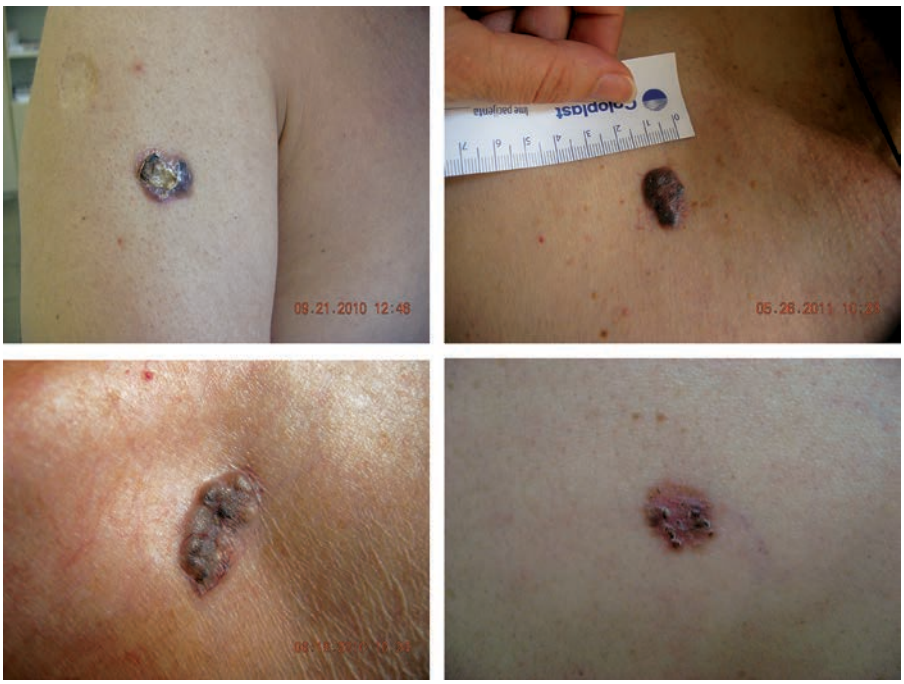

Figure 2. Main clinical types of BCC – a few features of the pigmented BCC

using polarized or nonpolarized light source, with or without application of immersion liquid. Further magnification and advances in analysis are possible by connecting a dermoscope to a digital camera and a computer.

First reported dermoscopic features of BCC were those observed in pigmented types (Figure 3): absence of pigment network, large gray-blue ovoid nests, multiple gray-blue globules, maple leaf like areas, spoke wheel areas, ulcerations and arborizing vessels (12). Main features of nonpigmented basal cell carcinomas (Figure 4) are bright red arborizing vessels distributed at the tumoral surface in a bizarre fashion, with stem vessels usually larger than 0.2 mm in diameter (13, 14). Dermoscopic features seen in superficial BCC (Figure 5) are shiny white to red areas, irregularly distributed short fine telangiectasias, and arborizing telangiectasias that are less than 0.2 mm in diameter (4, 15).

Reflectance confocal microscopy (RCM) is rather time-consuming and requires further expensive equipment**,** which makes it available only in specialized dermatologic centers in developed countries. RCM allows *in vivo* evaluation of horizontal tissue sections at near histological resolution, to the depth of 0.3 mm (superficial reticular dermis). Five major RCM diagnostic criteria for BCC are: elongated monomorphic basaloid nuclei, polarization of these nuclei along the same axis, prominent inflammatory infiltrate, increased dermal vasculature with tortuosity of the tumor vessels and pleomorphism of the overlying epidermis with loss of normal honeycomb pattern (16).

High-frequency ultrasound imaging (HFUI) uses a 20 MHz ultrasound transducer for examination of lesions to the depth of 6-7 mm, with axial resolution of 50 μm and lateral resolution of 350 μm. Skin tumors generally appear as a homogeneously echo-free areas in comparison to the surrounding echo-rich dermis. HFUI is capable of revealing the three-dimensional size of BCC, its margins and relation to adjacent vessels. Peritumoral fibrosis and inflammation may cause overestimation of BCC thickness, because they have the same echogenicity as the tumor (17, 18).

Histopathology features

Histopathology remains the "gold standard" in the BCC diagnosis and it requires biopsy (shave, punch, incisional or excisional) (1, 18).

Basal cell carcinoma originates from basaloid epithelium of the follicular infudibula or the distinct

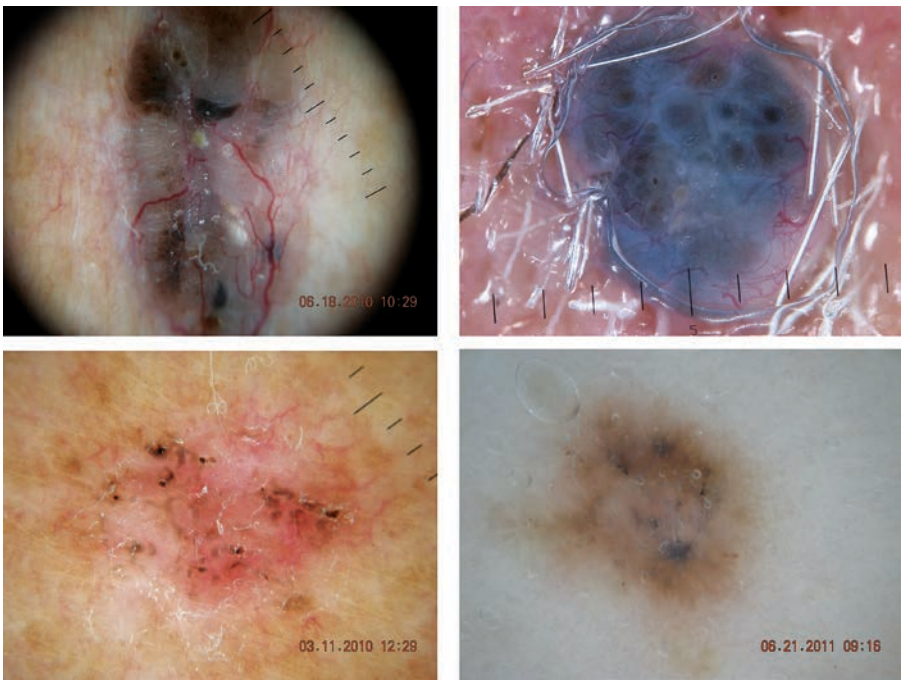

Figure 3. Dermoscopic features of pigmented BCCs

basaloid cells of the interfollicular epidermis (2). Predecessor stem cells are passing through the differentiation process along the follicular lines, so BCCs differentiate toward benign or malignant hair follicle tumors, sebaceous gland tumors, or apocrine gland tumors (19).

There is no unique and generally accepted classification of BCC, but most authors use two basic classification criteria for BCC: histological growth pattern, and histological differentiation (20).

In 2006, WHO published a classification of skin tumors which recognizes 8 histological types of BCC: superficial, nodular, micronodular, infiltrating, fibroepithelial, basosquamous, keratotic and basal cell carcinoma with adnexal differentiation (21).

According to the existing histological growth pattern, which is essential for prognosis, BCCs may be divided into circumscribed (low-risk) or diffuse (high-risk) types. High-risk types have greater probability of subclinical spread, aggressive local behavior, more frequent incomplete excision and local recurrence. Nodular BCC is a circumscribed undifferentiated tumor, while diffuse undifferentiated BCCs are superficial, infiltrative and micronodular (1, 20). Differentiated BCCs show a variety of specific cell lineage differentiation features that do not impact clinical behavior and prognosis (2).

Nodular BCCs consist of large aggregates of basaloid cells without adnexal differentiation. Basaloid cells are uniform in size with large nuclei; usually desmosomes can even be detected by light microscopy. At the periphery of aggregates cells have a parallel alignment, in a picket fence arrangement called palisading. The surrounding stroma shows myxoid changes, while tissue processing creates artificial slit-like retractions between nests of tumor cells and the stroma (1).

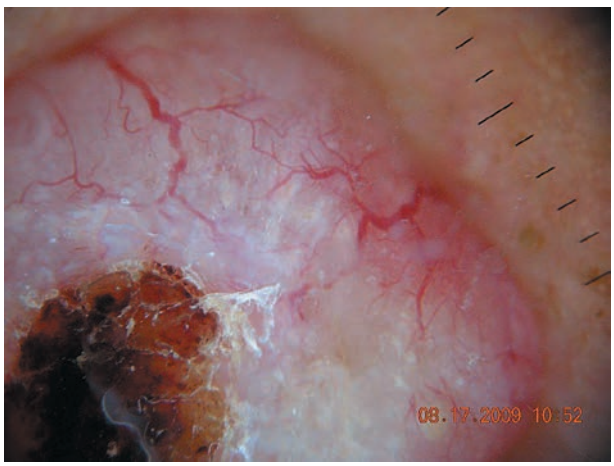

Figure 4. Dermoscopic features of nonpigmented nodular BCCs

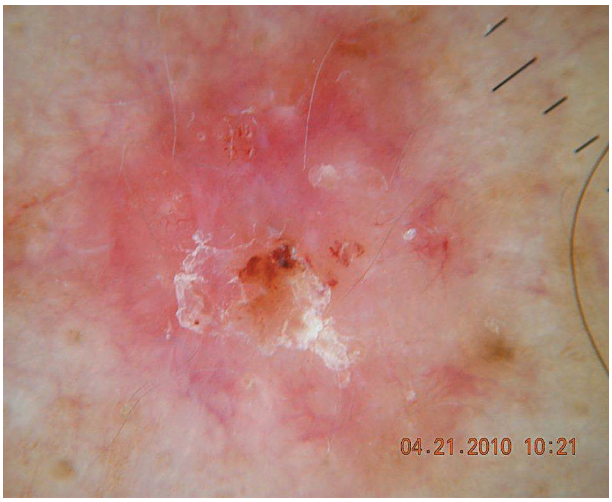

Figure 5. Dermoscopic features of nonpigmented superficial BCCs

In superficial BCC, proliferation of atypical basaloid cells forms an axis parallel to the epidermal surface, myxoid stroma causes artificial retractions, and frequently band-like lymphoid infiltrates are present (2).

Infiltrative BCCs exhibit non-sclerosing and sclerosing (morpheaform) histological variants – irregular, elongated and angulated nests of tumor cells without palisading widely separated by mucinous, edematous or fibrotic stroma, while mitotic activity and individual cell necrosis are frequently seen (2, 20).

Micronodular BCC is made of small, round aggregates of basaloid cells with palisading, but with a tendency of asymmetrical deep infiltration and autonomous growth outside the stromal borders (1). Some authors believe that the micronodular type may be included into the nodular or infiltrative types (20).

Fibroepithelial BCC or fibroepithelioma of Pinkus is characterized by an arborising network of cords of basaloid cells that surround the fibrovascular stroma (21).

Keratotic BCC has overall architectural features of a nodular BCC, with prominent keratin formation in the center of tumor islands (21).

Basal cell carcinoma with adnexal differentiation may show follicular, eccrine or apocrine differentiation (21).

In less than 2% of all skin cancers, histopathological examination reveals a controversial entity of basosquamous carcinoma - BSC, defined by an infiltrative growth of basaloid cells larger than those of classic BCC, with scant cytoplasm and large, uniform and pale nuclei. Basaloid cells form clusters within which focal aggregates of squamous cells are found, either near the center (intermediary type) or scattered throughout the lesion (mixed type). Peripheral palisading is rare, with minimal stromal retraction. BSC is an extremely agressive tumor, its growth is infiltrative, recurrences and metastases are frequent. Basosquamous carcinomas should be differentiated from the basaloid squamous cell carcinoma that originates from the upper aero-digestive tract (oral and nasal cavity, pharynx or larynx) (2, 22, 23, 24).

Full-thickness biopsy of the tumor is recommended, because biological transformation of BCC tends to occur at the base and edges of the growing neoplasm, causing shave and punch biopsy specimens to have an intrinsic error rate of roughly 20% in comparison to complete excisions (2). In a review of 1039 consecutive cases of basal cell carcinoma, Sexton et al. classified them into 6 histological types, and found that more than a third (38.6%) of analyzed tumors had mixed histology, 21% were solely nodular, 17.4% superficial, 14.5% micronodular, 7.4% infiltrative and 1.1% morhoeaform (2, 6). Unrecognized histological mixtures of indolent and aggressive forms may be responsible for unexpected tumor recurrences. BCCs with mixed histology patterns are most frequently found in the head and neck region, while almost half of these have nasal localization (25).

Presence of melanin is not unusual, either within the tumor itself, or in the surrounding dermis. The tumor mass often contains hyperplastic melanocytes, and malignant epithelial cells often take over their melanosomes, while dermal melanin is mainly inside the melanophages (12).

Tumor stroma infiltration of BCCs mostly consists of T-helper lymphocytes, and the presence of plasma cells is connected to tumor exulceration (2). Dense band-like lymphocyte inflammatory infiltrates create a peritumoral hypo- or hyperpigmentation which is referred to as the "halo" BCC (2).

Treatment options

Treatment goals include tumor excision, preserving healthy tissue and function while obtaining optimal cosmetic result. Treatment options are numerous and the choice depends on : patient's age and overall health status, tumor size, histology type, location,

number of tumors, and whether the tumor is primary or recurrent (1).

Treatment outcome depends on the immunological status of the patient, biological behavior of the tumor, and chosen treatment modality (25). Treatment modalities may be administered as mono therapy or combined therapy. The following treatment options are currently recognized:

Surgical excision (Figure 6) is considered to be a first line treatment option; the percentage of recurrences varies between 2-10% in different studies and depends on the histological type of the tumor (25). The recommended surgical margins for primary BCC of less than 20 mm in diameter are 3-5mm. For larger and recurrent lesions and for aggressive histological subtypes, the margins are wider – 10 mm into healthy tissue (1).

Tumor margins are marked with a skin marker prior to injection of the local anesthetic, as sometimes this makes valid detection of margins difficult (1). The sample is fixated in 10% formalin solution. In the pathology laboratory a paraffin mold is made, then sliced in vertical sections and formed into slides that are examined by a pathologist who reports the type of tumor and extension of tumor to the free margins.

Vertical sections are the standard of histology examination in surgical excision, but depending on the sectioning method used – e.g. bread loafing, they allow only representative parts of the sample to be examined, which is not more than 50% of the total depth and lateral margins of the tumor. This explains the recurrence of adequately treated BCC with the histology report of uninvolved free margins (26, 27).

In cases of incomplete excision histology reports, the analysis on the palisading pattern of tumor can help in making a decision pro or against reexcision. It was found that BCC with a histologically regular palisading pattern very rarely metastases even if incompletely excised (26).

Complications of surgical ("cold steel") excision are: bleeding, infection, suture reaction, hypersensitivity, contact dermatitis, dehiscence, necrosis, surface contour irregularity, nerve injury, milia, telangiectasias, hypergranulation, pruritus, ectropion, eclabium, chondritis, scarring. Serious postoperative complications arising from dermatologic surgery are generally uncommon. Surgical complications are anticipated and addressed as soon as surgical treatment is determined to be necessary, usually during the preoperative consultation (28).

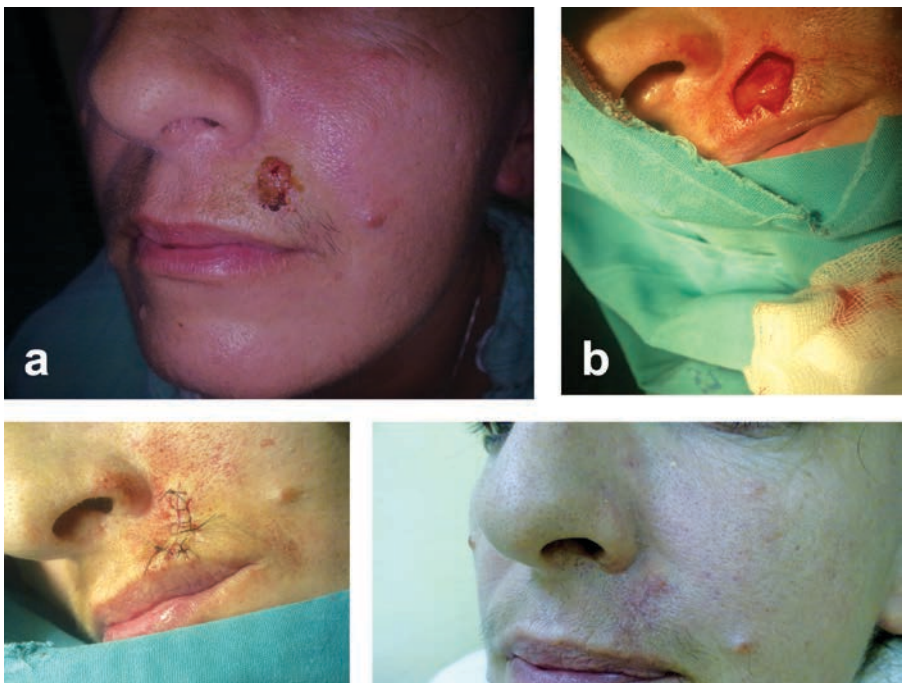

Figure 6. A patient with nodular BCC a) before; b) during; and c) after surgical excision using M-plasty technique; d) one week following suture removal

Mohs micrographic surgery is an elegant, complex and effective technique for removing a wide variety of continually growing skin and mucosal cancers, with high effectiveness and minimal tissue loss. Mohs surgery requires multiple, interdependent surgical, laboratory, and pathology steps that are usually performed by one or more persons over an extended period of time. It is a time consuming and an expensive procedure that requires highly skilled personnel and relatively demanding equipment and settings (29). Multiple horizontal frozen sections of tumor are obtained and microscopically examined before the final tumor margins are reached (1). Depending on the site, the type and extensions of the tumor, in some instances multidisciplinary approach is required – ophthalmic, plastic, orthopedic, oncologic etc. The delayed Mohs surgery is a modified Mohs surgery technique where the first stage layer specimen is fixed in paraffin and the histology report is awaited (for a day or two) before the next section is taken (26).

Indications for Mohs micrographic surgery of BCC include: recurrent tumors, incomplete tumor excision, primary BCCs of high-risk areas, tumors with rapid and aggressive growth, size greater than 20mm, cosmetic considerations - especially in young patients, tumors in immunosuppressed patients, tumors of indistinct clinical margins, neglected tumors, tumors arising in scars or in previously irradiated skin, tumors in nevoid BCC syndrome patients (1, 29). Complications of Mohs surgery are consistent with other skin surgeries in general, the cure rate is high and the recurrence rate is very low, ranging 1.0-3.3% (25).

Cryosurgery, usually accompanied by prior curettage of the tumor, is used mostly in cases of nodular tumors not larger than 2 cm in diameter, with clinically clearly defined borders located at the skin above the bone or cartilage, unless the tumor is fixated to the underlying structures. This method is suitable for the treatment of multiples lesions. Necessary equipment includes a cryo-bottle with liquid nitrogen and adequate applicators (cryoprobes). Cryosurgery is usually performed in two 30 seconds freeze-thaw cycles during one session, and it may be monitored by thermocouples (temperature sensors). Cosmetic results are unpredictable, with possible prolonged edema, dyschromia, scar formation and neuropathy from adjacent nerve injury, especially on the digits or elbows. Contraindications for cryosurgery are susceptibility to cold – cryoglobulinemia, cold panniculitis, Raynaud syndrome, etc (1, 26, 27).

Currently, basal cell carcinomas are also managed by using novel technologies, such as radio frequency and laser photothermal ablation. Debulking of skin cancers with radio frequency before cryosurgery, or even excision with radio frequency followed with mild curettage is advocated by some authors (30, 31). Moreover, superficial basal cell carcinomas have been effectively treated with laser ablation, although this is unlikely to be the treatment of choice (32).

Electrodessication with prior curettage is performed in several cycles of therapy with the best results in small BCCs (diameter up to 10 mm) located on the trunk and limbs, but may provoke intense scarring at the place of application (1, 27).

Radiation therapy is generally reserved for patients inappropriate for more aggressive treatment, elderly and those in a poor health condition, for large tumors at locations difficult for surgical treatment. Superficial X ray therapy (Figure 7), using soft X rays with safety margins of 10 mm, gives good results in lesions up to 6 mm in depth. Electron beam therapy demonstrates increased tissue penetration, so it is suitable for deeper tumors. Brachytherapy is useful for lesions at curved surfaces, and may be applied as an interstitial brachytherapy with γ-ray emitting sources or as a synthetic resin containing radioactive β-emitting isotopes. In order to achieve an adequate cumulative dose of irradiation, treatments are done in several cycles. Radiation causes significant skin scarring, atrophy and telangiectasias, sometimes with very poor esthetic outcome. Due to the risk of carcinogenesis at irradiation sites, repeated radiation therapy is contraindicated. Other contraindications are genodermatoses and collagenoses related to higher risk of developing carcinomas (1, 26, 27, 33).

Photodynamic therapy (PDT) is based on synergistic activities of topically applied photosensitizers, most commonly aminolevulinic acid (ALA), oxygen, and an appropriate source of visible light, which cause cytotoxic reaction. The treatment cycle consists of two PDT sessions separated by one-week interval. The treatment may be repeated after 3 months of follow up, if lesions are not completely cleared and partial response is evident. Topical ALA-

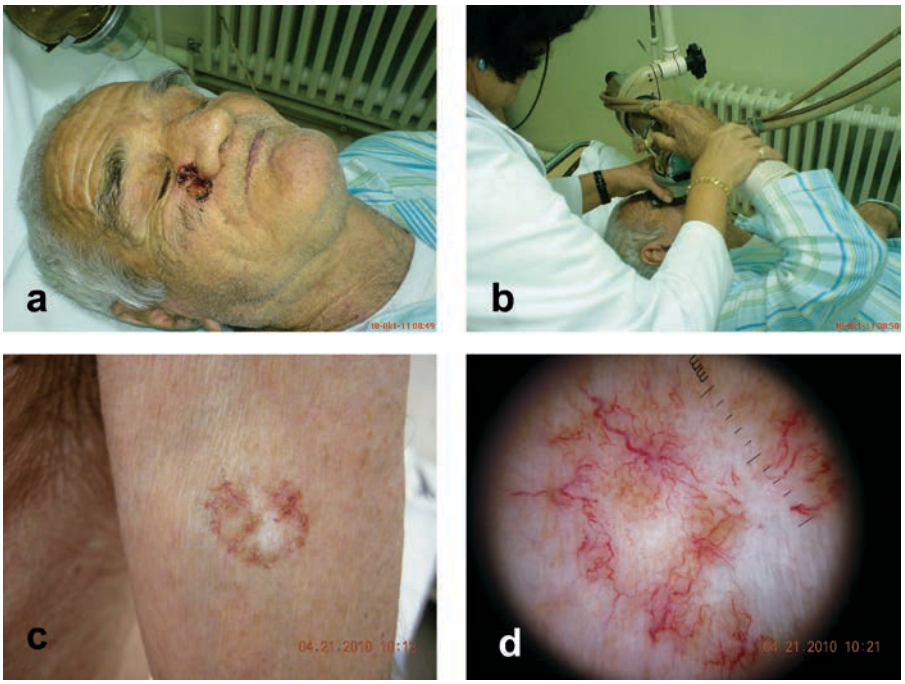

Figure 7. Superficial X-ray therapy tube application (a,b). Postirradiation scarring, atrophy and telangiectasias – c) clinical; and d) dermoscopic view

PDT demonstrated excellent cosmetic results and is useful in the treatment of multiple lesions. So far, results demonstrated safety in the treatment of superficial BCC, but some studies reported success of ALA-PDT in treating nodular BCCs with a mandatory prior curettage. PDT is contraindicated in patients with porphyria and patients with photosensitivity to wave lengths of applied light sources (26, 27, 34).

Pharmacological treatment refers to topical application of 5% imiquimod cream during several weeks (six to twelve). This immune response modifier is currently officially accepted in the treatment of superficial BCCs, with recommended dose regimen: once a day (in the evening) during five successive days of the week, within a six week period. Imiquimod cream may be combined with other treatment options (in order to decrease the tumor size, and thereby decrease postoperative deficits). Topical 5% imiquimod application causes tissue inflammatory reactions, such as: erythema, erosions, crusts, sometimes accompanied itching or burning sensations (26, 35).

Most severe cases of non-treated or inadequately treated aggressive BCCs at risky locations may lead to invasion of orbital region, ethmoid or frontal sinus, and finally to lethal outcome. Treatment of such cases includes systemic chemotherapy, as a palliative method or preoperative multidisciplinary approach. The most effective chemotherapeutic agent appears to be cysplatin, with an average therapeutic response of about 70%, but the number of reported cases is rather small (36).

Hopes for successful treatment of advanced BCCs are invested in vismodegib (GDC-0449), a small, orally administrable molecule belonging to 2-arylpyridine class molecule, acting as an competitive antagonist of the smoothened receptor (SMO) which is a part of the hedgehog (HH) signaling pathway, pathogenetically relevant in most basal-cell carcinomas (37, 38).

Other treatments, in the phase of investigation, are topical usage of 0.005% solasodine glycoalkaloids, 0.1% tazarotene, destruction of BBC with hyperthermia produced by continual Nd:Yag laser, and intralesional bleomycin injection followed by local electric pulses to the tumor (39, 40, 41, 42).

Prevention

The primary prevention strategies for BCC, and for skin cancers in general, are focused on behavioral modifications to minimize exposure to risk factors, especially UV radiation, including sun avoidance, use

of sun screens with high SPF (sun protective factors) for Ultraviolet B (UVB) filters as well as with UVA filters, wearing protective clothing, and screening for early tumor detection (43).

Beyond standard sun-protection measures, chemopreventive agents offer the possibility of enhanced non-melanoma skin cancer (NMSC) prevention in high-risk patients. An ideal chemopreventive agent should be effective with minimal toxicity to normal cells. Retinoids are the most thoroughly researched NMSC chemopreventive agents that have proven efficacy (44).

Selection of an oral, retinoid, chemopreventive agent depends on comorbidities: isotretinoin is used more often in patients with xeroderma pigmentosum and Gorlin-Goltz syndrome, and acitretin is prescribed for transplant patients, patients with psoriasis and with sun damage. The dose of retinoids is gradually increased up to 0.25 – 0.5 mg/kg BW for isotretinoin and 10-25 mg daily for acitretin, and may be adjusted in relation to side effects. The commonest side effects are dry skin and mucosal membranes, elevation of liver function tests and serum lipids. Most of the side effects are dose dependant and usually subside during the treatment. The above mentioned dose span is well tolerated for a prolonged period of time (45). Retinoids are teratogenic and they should be prescribed to female patients at childbearing age with extreme caution.

Follow-up

Regular follow-up of patients once diagnosed with BCC is necessary in order to identify possible recurrences and new BCCs. The study of Van Iersel et al. showed that there is an increased risk for the development of a subsequent BCC in 28% of patients with a single BCC, and in 40% of patients with multiple BCC during a 5-year follow-up. The authors also identified higher risk in older patients, those with multiple BCC at first presentation, and those with tumors larger than 1 cm in size or infiltrative histology type. The correlation between the incidence of successive BCC and gender, tumor location or depth was not found (46).

Regular follow-ups are also important in the prevention, aimed at educating patients in self examination, sun protection and avoidance of other risk factors. At each follow-up visit, full skin examination needs to be performed. The frequency of follow-up visits differs within different health systems and depends on the compliance of patients that generally reduces the time; they range from 1 to 3 years for low risk BCC to 5 years for high risk or multiple BCCs (47).

Authors currently recommend the first follow up visit 3-6 months after excision, the second visit 6 months later, and afterwards annually for 5 years.

Conclusion

Basal cell carcinoma is a frequent challenge for dermatologists and therefore it should not be underestimated. Although we may seem to know a lot about this type of cancer, it never ceases to surprise. The essential health strategy should be focused on prevention, early detection, further research on BCC biology, and efficient treatment options.

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Bazocelularni karcinom: čest izazov

Sažetak

Uvod: Bazocelularni kacinom (BCK) je spororastući maligni epidermalni tumor koji se pretežno javlja na fotoeksponiranim regijama kože kod pripadnika bele rase.

Epidemiološke karakteristike i faktori rizika: BCK čini oko 80% svih dijagnostikovanih karcinoma kože u svetu, sa konstatntnim porastom incidencije. Uglavnom oboljevaju starije osobe, nakon pete decenije života. Broj novih slučajeva ovog karcinoma najveći je u Australiji - preko 730 na 100 000 stanovnika godišnje. Prema podacima Registra za maligne neoplazme Vojvodine u petogodišnjem periodu 2004 - 2008. godine prosečna godišnja incidencija BCK iznosila je 27,44 na 100 000 stanovnika, ali u našem zdravstvenom sistemu ne postoji obaveza prijavljivanja BCK pa je realno pretpostaviti da je incidencija veća od registrovane. Najznačajniji etiološki faktor za nastanak BCK je hronična izloženost ultravioletnom (UV) zračenju, a doprinoseći etiološki faktori su uglavnom konstitucionalni.

Patogeneza i biološko ponašanje: UV zračenje izaziva lokalnu imunosupresiju i mutacije gena koje dovode do poremećaja aktivacije "hedgehog" signalnog mehanizma u ćelijama, i time do transformacije adultnih stem ćelija u stem ćelije karcinoma. Ispitivanjem genoma BCK utvrđene su mutacije gena p53, Bcl-2 i PTCH gena. Metastaze su izuzetno retke (u 0,0028% do 0,5% slučajeva), ali je BCK lokalno invazivan i može izazvati značajnu destrukciju okolnih tkiva, oštećenje njihove funkcije i estetike. Bazocelularni karcinom širi se u pravcu najmanjeg otpora okolnih tkiva, tako da tumorske ćelije progrediraju duž periosta, perihondrijuma, perineuralno ili duž fascije.

Kliničke karakteristike: Približno 85% BCC razvija se u predelu glave, zbog intenzivne fotoekspoekspozicije ove regije. Subjektivne tegobe su uglavnom odsutne, a retko prisutna bolna osetljivost ukazuje na perineuralnu infiltraciju. Razlikuju se četiri osnovne kliničke forme: nodularni, superficijalni, pigmentni i morfeaformni. Klinička podela nije od značaja za prognozu. Sindrom nevoidnog bazocelularnog karcinoma (Gorlin Goltz sindrom) nasleđuje se autozomno dominantno, a karakteriše se razvojem brojnih BCK tokom života, epidermalnim cistama na koži, palmoplantarnom "pitted" keratolizom, odontogenim cistama vilice, anomalijama skeleta i drugih organskih sistema.

Neinvazivne dijagnostičke metode: U kliničkoj preselekciji suspektnih BCK i planiranju tretmana značajnu primenu su našle neinvazivne dopunske dijagnostičke metode: dermoskopija, konfokalna mikroskopija i visokofrekventni ultrazvučni imidžing.

Histopatološke karakteristike: Histološki pregled tkiva i dalje je „zlatni standard" dijagnoze. Prilikom biopsije preporučuje se uzimanje isečka čitave debljine tumora jer se biološka transformacija BCK dešava pri bazi i na rubovima tumora, a utvrđeno je i da BCK često ima mešovitu histologiju. Ne postoji jedinstvena histološka klasifikacija BCK, ali većina autora koristi dva osnovna kriterijuma: histološki obrazac rasta i histološku diferencijaciju. Poslednja klasifikacija koju je objavila SZO datira iz 2006. godine i razlikuje 8 histoloških tipova BCK: superficijalni, nodularni, mikronodularni, infiltrativni, fibroepitelijalni, bazoskvamozni, keratotični i BCK sa adneksalnom diferencijacijom. Od prognostičkog značaja je histološki obrazac rasta tumora, prema kojem se razlikuju cirkumskriptni (nisko-rizični) i difuzni (visoko-rizični, agresivni) bazocelularni karcinomi.

Terapija: Lečenje BCK treba da zadovolji sledeće ciljeve: uklanjanje tumora, očuvanje zdravog tkiva, očuvanje funkcije, optimalni kozmetski rezultat. Terapijski modaliteti su brojni, mogu se primenjivati kao monoterapija ili se kombinovati, a izbor zavisi od životne dobi i opšteg zdravstvenog stanja pacijenta, brojnosti tumora, lokalizacije i prečnika tumora, histološkog tipa, od toga da li je u pitanju primarni ili rekurentni tumor. Hirurška ekscizija se smatra metodom prvog izbora. Za primarni BCK prečnika do 2 cm, koriste se hirurške margine širine 3-5 mm, a za veće i rekurentne BCK, kao i za BCK histološki agresivnog ponašanja, margine širine 10 mm klinički nezahvaćenog tkiva. Standardne vertikalne sekcije tkiva omogućavaju pregled samo reprezentativnih delova perifernih i dubokih hirurških margina, što u najboljem slučaju ne prevazilazi 50% ukupnih margina, čime se objašnjavaju recidivi tumora koji su prema izveštaju patologa bili u potpunosti odstranjeni.

U slučaju inkompletne ekscizije, od pomoći u odluci o potrebi reekscizije može biti analiza izgleda palisadnog sloja tumora – BCK čije su ćelije pravilno palisadnog rasporeda veoma retko recidiviraju, iako nisu kompletno hirurški uklonjeni.

Mohs-ova mikrografska hirurgija predstavlja kompleksnu hiruršku tehniku kojom se ostvaruje maksimalna efektivnost u odstranjivanju tumora uz minimalan gubitak zdravog tkiva. Zasniva se na mikroskopskom pregledu multiplih smrznutih horizontalnih sekcija tumora do dosezanja njegovih krajnjih margina. Ova tehnika zahteva posebno obučen kadar, opremu i značajan utrošak vremena, što je čini veoma skupom. Najznačajnije indikacije su agresivni, rekurentni ili inkompletno ekscidirani tumori, tumori prečnika preko 20 mm, kao i tumori rizičnih lokalizacija.

Kriohirurški tretman, najčešće sa prethodnom kiretažom tumora, koristi se uglavnom kod nodularnih BCK prečnika do 2 cm, klinički dobro definisanih granica, na lokalizacijama kože iznad kosti ili hrskavice ukoliko tumor nije fiksiran za navedene strukture. Elektrodesikacija sa prethodnom kiretažom tumora najbolje rezultate daje kod BCK prečnika do 1 cm, lokalizovanih na trupu i ekstremitetima.

Novije tehnike u oblasti dermatohirurgije se odnose na primenu radiofrekventne i laserske fototermalne ablacije.

Radiološka terapija uglavnom je rezervisana za starije pacijente čije opšte zdravstveno stanje ne dozvoljava agresivnije intervencije, velike tumore na lokalizacijama koje se hirurški teško tretiraju. U ovoj oblasti primenu su našle površinska radioterapija (pogodna za lezije do dubine od 6 mm), elektron bim terapija (ima veću dubinu penetracije u tkiva), i brahiterapija (pogodna za lezije na zakrivljenim površinama). Kontraindikovano je ponavljati zračenje tumora koji su recidivirali nakon radioterapije.

Topikalna fotodinamska terapija i aplikacija 5% imiquimod krema pokazale su odličan kozmetski ishod, pogodne su za tretman multiplih superficijalnih BCK lezija.

U tretmanu najtežih slučajeva BCK, sa invazijom orbite ili sinusa, dolazi u obzir sistemska hemioterapija gde se najefikasnijim pokazao cisplatin.

Tretmani u fazi istraživanja su peroralna primena vismodegiba, lokalna primena 0,005% solasodin glikoalkaloida, lokalna primena 0,1% tazarotena, destrukcija BCC hipertermijom koju produkuje kontinuirani Nd:Yag laser, i tretman tumora električnim pulsevima nakon intralezionalnog ubrizgavanja bleomicina.

Prevencija: Strategije primarne prevencije odnose se na izbegavanje uticaja faktora rizika, naročito prekomerne izloženosti UV zračenju. Sekundarna prevencija označava rano otkrivanje BCK skrining pregledima. Kod pacijenata pod povećanim rizikom nastanka nemelanocitnih karcinoma kože dolazi u obzir hemoprevencija oralnim retinoidima.

Praćenje obolelih: Nakon sprovedene terapije BCK, neophodno je vršiti periodične kontrolne preglede zbog monitoringa mogućih recidiva, rane detekcije novih tumora i edukacije pacijenata. Praksa je različita, na Klinici za kožno-venerične bolesti u Novom Sadu nakon hirurške ekscizije praktikujemo kontrole na 6 meseci tokom prve godine, potom jedanput godišnje tokom ukupno 5 godina.

Zaključak: BCK ne treba potceniti jer predstavlja izazov sa kojim se često susrećemo. Neophodna je osnovna strategija bazirana na prevenciji i ranoj detekciji ovog tumora, kao i dalje istraživanje njegove biologije i efikasnih tretmana.

Ključne reči

Bazocelularni karcinom + dijagnoza + klasifikacija + terapija + hirurgija; Faktori rizika; Kombinovana terapija; Lokalni recidiv neoplazmi; Dijagnoza; Ishod lečenja

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Basal cell carcinoma: a retrospective clinicopathological analysis of 100 cases derived from the Histopathological Registry of the Institute of Pathology in Niš

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VERSITA

Abstract

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin. This study was conducted to analyze patients with BCC, their age and sex distribution, occupation, site distribution of tumors, clinical types, and histopathological characteristics of lesions. Based on the data obtained from the Histopathological Registry, a clinical and histopathological analysis of the surgically excised BCCs was performed.

The study included 100 randomly selected patients out of 263 consecutive patients with histopathologically diagnosed BCC at the Institute of Pathology of the Clinical Center in Niš in the period of 15 months. The sex ratio was 1.4:1 in favor of men ($p<0.05$). Two thirds of patients were over the age of 60 ($p<0.0001$). The average age of patients was 66.6 ± 12.2 years (range 23 – 90). In agreement with the age distribution, 53 patients were retired (mostly retired farmers), 12 were workers, 14 farmers, 12 without permanent employment, 5 were housewives, and 4 clerks. A substantial majority of 61% of examinees lived in the country ($p<0.001$). The employment status was related to the age of examinees, but also with the altered demographic structure in the country: many workers lived in the country, or returned to the country after retirement.

BCC was commonly found on the face (77%), and rarely on the trunk (11%) and extremities (2%).

There were no data about exposition to X-rays or chemicals (except for pesticides and insecticides), scars resulting from burns or genodermatoses. In 87% of cases, BCC was significantly most often found at sites continually exposed to the sun (head including face and scalp, and neck). The most commonly diagnosed was the nodular type (57%), then the superficial (7%), ulcerative (5%), ulcero-sclerotic (4%), pigmented (1%), and morpheaform (1%). In 27% of cases, there were no data about the histopathological type of BCC in the Histopathological Registry, based on which accurate histological type of BCC could have been established. Based on histopathological analysis, apart from the nodular (40%), other types were rarely diagnosed, like the adenoid (12%) ($p<0.0001$), mixed types (nodular-adenoid, nodular-adenoid-fibroblastic and mixed) (9%), superficial (7%), fibroblastic (2%), infiltrative (1%), pigmented (1%), and morpheaform (1%). Surgical excision is the gold standard in the treatment of BCC: conventional, conducted in our patients, and Mohs micrographic surgery, which takes an important place in the treatment of high-risk BCCs. In 6% of cases, the tumor process was found in the margins of the excision.

In conclusion: Basal cell carcinoma was more common in males than in females. Significantly more patients with excised basal cell carcinoma lived in the country. An age-related increase in the number of patients with BCC has been established, and most patients with excised basal cell carcinomas belonged to the age group of 61 to 81 years of age. In most patients the tumor site was on the face, whereas clinically and histopathologically, nodular type was the most common.

Key words

Carcinoma, Basal Cell + diagnosis + classification + etiology+ epidemiology; Skin Neoplasms + surgery; Age Factors; Neoplasms by Site; Sunlight

Basal cell carcinoma (BCC) is the most common malignant tumor of the skin. It is composed of cells similar to those in the basal area of the epidermis and the matrix cells of the skin appendages. Tumor cells originate from pluripotent cells of the basal layer of the epidermis, of the outer rooth sheat of the hair follicle, sebaceous and sweat glands (1, 2, 3). BCC is a malignant tumor of the follicular germinative cells (4). BCC is a slow growing neoplasm which shows minimal invasion to the soft tissue. Sometimes, however, BCC is characterized by aggressive growth, deep invasion, local recurrence and metastases (5, 6). Metastatic BCC is extremely rare, occurring in 0.0028% to 0.55% of all BCCs. This low rate is believed to be because the tumor cells require supporting stroma to survive (7). The histological variability originates from the pluripotentiality of immature cells of the epidermis (1).

BCC is more common in males than females: the annual incidence for males and females ranges from 175 to 849 and 124 to 605 per 100000 people, respectively (8,9,10). In Australia, it is three times more common than any other skin cancer (11). The comparison of age-specific incidence rates of BCCs in two studies from Sweden and Australia indicate that its rate in northern Europe is approximately three to four times lower than that estimated in Australian population [11,12,13].

Most investigations indicate that BCCs account for more than 70% of cases of NMSC (non-melanoma skin cancer). In non-immunosuppressed, fair-skinned individuals, a ratio of 4:1 between BCC and SCC (squamous cell carcinoma) incidence rates has been described as a relatively constant, but this ratio differs between countries with low and high ambient sun exposure. With increasing sun exposure, there is a disproportionate increase in SCC in relation to BCC (1).

The prevalence of skin cancer like BCC depends on the population susceptibility, skin type and exposure to ultraviolet radiation (1, 14), but also on other factors such as ionizing radiation, chemical carcinogens (arsenic found in insecticides), scars from previous diseases or burns, long-term ulcers on the lower extremities, some genodermatoses such as albinism, xeroderma pigmentosum, Rombo syndrome (basall cell carcinoma, atrophoderma vermiculata, milia, hypotrichosis, trichoepithelioma, and peripheral vasodilatation), Bazex's syndrome (basall cell carcinoma, follicular atrophoderma, hypotrichosis, localized ahidrosis), Gorlin's syndrome (basall cell carcinoma, palmoplantar pits, odontogenic keratocysts, bifid ribs, frontal bossing, and central nervous system defects), immunodeficiency, as well as some therapeutic procedures (2, 15-19). The role of human papillomavirus (HPV) in the development of BCC in immunocompromised persons requires further research (20).

Although the exact incidence of BCC is unknown, it clearly differs in regard to geographical regions (21), type of skin, long-term sun exposure and progressive aging of the population (22). According to statistical data, the incidence of BCC in Netherlands in 1999 was 53 men and 38 women per 100000 inhabitants (23), whereas in 2004 it increased to 93 men and 82 women per 100000 inhabitants (24). In France, 70 new cases are registered annually per 100000 inhabitants (25). In Germany, in the period 1998 – 2003, the incidence for men was 112, and 118 for women per 100000 inhabitants (26). The incidence of BCC increases by 10% each year (27).

In 1986, there were 112 (59 male and 53 female) histopathological examinations for BCC at the Institute of Pathology in Niš, whereas in 1996 there were 207 (113 male and 94 female) – nearly double in 10 years time (28). In the municipality of Niš, in 1990 there were 113 (75 male and 38 female) patients with non-melanoma skin cancer, and in 2000, there were 229 (124 male and 105 female) (29). The number is probably much higher, since not all patients were registered.

We may only presume just how high the prevalence of BCC will be, knowing about the depletion of the ozone layer, which is known to absorb most of the harmful ultraviolet B and C radiation (30), while it is estimated that in 2015, in Europe, there will be 50 million people older than 80 years of age (31).

The aim of this clinicohistopathological analysis is to establish clinical and pathological characteristics of basal cell carcinomas diagnosed at the Institute of Pathology of the Clinical Center in Niš.

Material and methods

The study included 100 randomly selected patients out of the total number of out of 263 consecutive patients with histopathologically established basal cell

carcinoma at the Institute of Pathology of the Clinical Center in Niš in the period of 15 months. Based on the data obtained from the Histopathological Registry, a clinical (demographic data, anamnesis, clinical picture), and histopathological analysis of surgically excised tumors (routine staining techniques including haematoxylin and eosin – H&E, periodic acid–Schiff-PAS, and Van Gieson staining) were performed.

Statistical methods included the T-test of significance for difference in percentages, χ^2 test for testing and comparing random distribution of frequencies, as well as the test of statistically significant deviation of obtained data in the contigency table of theoretical frequencies.

Results

Out of 100 patients with BCC who were included in this study, 58 were men and 42 women (male to female ratio 1,4: 1) (Table 1). The difference between the percentage of men and women with BCC was statistically significant $p<0,05$. The average age of patients was 66.6 ± 12.2 years. The youngest patient was a female patient aged 23 with a BCC on her face, and the oldest patient was a man aged 90, also with a facial tumor. Most patients were over 60 years of age, that is 75% of the total number of examined patients with BCC (Table 1). The age distribution of patients shown in Table 1. significantly differs from random distribution, due to an increased number of aged patients ($\chi^2(7)=97.6$; $p<0.0001$).

In accordance with the age distribution, 53 patients were retired, 12 workers, 14 farmers, 12 without permanent employment, 5 housewives, and 4 clerks. Among the retired, many used to be farmers, both men and women. Thirtyeight patients resided in the town, and 62 in the country. The difference between patients from the town and from the country is statistically significant $p<0.001$.

Table 1. Demographic characteristics of patients with basal cell carcinoma (n=100)

Patients	Number (n=100)
Male:Female	1,4:1
Age (years)	
<20	0
21-30	3
31-40	0
41-50	6
51-60	16
61-70	36
71-80	27
>80	12
Occupation	
Retired	53
Indoor workers	12
Farmers	14
Without permanent employment	12
Housewives	5
Clerks	4
Place of residence	
Town	38
Country	62

Table 2. Distribution of basal cell carcinomas by site

Location	Number (n=100)
Continually sun-exposed areas	87
H-zone	48
Nose	29
Periorbital region	10
Ear area	2
Forehead	3
Cheek	2
Lip	1
Chin	1
Face (not specified)	29
Neck	5
Scalp	5
Frequently sun-exposed	2
Dorsal hand surface	1
Shoulder	1
Non-sun-exposed	11
Trunk	4
Lower extremity	1
Back	6

Sun exposure was certainly professional for a great number of examinees, because many of them were employed in factories and worked on farms, but also recreational and/or both.

There were no data about exposition to X-rays and chemicals (except for pesticides and insecticides), burn scars or genodermatoses.

BCCs were most commonly found in continually sun-exposed skin areas (87%), than on the trunk (11%), and on extremities (2%) (Table 2). Head and neck are considered to be continually sun-exposed. The most common site of BCC was the face in 77 persons, mostly in the H-zone in 48 patients (Table 2).

In regions which are frequently, but not continually sun-eposed, BCC was found in 2 patients: on the dorsal hand surface in one patient, and ~~one~~ on the shoulder in another. In non-sun-exposed regions, BCC was found in 11 patients: 4 on the trunk, 1 on the leg, and 6 on the back. The percentage of patients with BCCs found on continually sun-exposed regions (87%) significantly differed from the percentage of patients with BCCs on non-sun-exposed regions (11%), with high significance ($p<0.0001$), whereas the percentage of patients in the second group (BCCs on non-sun-exposed regions) was significantly higher than in patients with BCCs in regions which are not frequently, but often sun-exposed (2%), $p<0.05$.

Table 3. shows the site and age distribution of patients with BCC. There were only 9 patients with BCC under the age of 50 years, and all 9 (100%) had head and/or neck tumors. There were 12/16 (75%) of patients aged 50 – 60 years with BCC, also located on the head and/or neck; 28/36 (77.7%) patients aged 60 – 70 years, 27/27 (100%) aged 70 – 80 years, and 11/12 (91.66%) in the nineth decade of life.

Table 3. Distribution of basal cell carcinoma regarding its site and age of patients

Age (years)	Location			Total (n=100)
	Head and neck	Trunk	Extremities	
21-30	3	0	0	3
31-40	0	0	0	0
41-50	6	0	0	6
51-60	12	3	1	16
61-70	28	7	1	36
71-80	27	0	0	27
>80	11	1	0	12
Total	87	11	2	100

The distribution of patients with BCC located on the head and/or neck, regarding their age, does not significantly differ from the distribution of patients with BCC located on the trunk or extremities ($X^2(5)=6.18$; $p<0.05$ with Yates correction). The greatest number of patients with both locations was aged between 61 – 70 years.

Testing the difference between the obtained distribution of all patients in regard to the site of lesions in certain age groups and the theoretical distribution expected based on probability showed a statistically significant result ($X^2(6)=72.86$; $p<0.0005$). The greatest deviation of the random distribution of patients occurred in the group of patients aged between 61 and 80 years.

Table 4. shows results related to the frequency of certain clinical and histopathological types of BCC. The most common type was the nodular type (Figure 1), without or with ulcerations, in a total of 57 patients (Table 4), which was significantly more frequent than all the other types together (43%) ($p<0.05$), whereas there were significantly more ($p<0.01$) nodular tumors without (38%) than with ulcerations (19%) (Figure 2). Ulcerative type (Figure 3) was found in 5 patients, and 4 presented with ulcerosclerotic type (Figure 4). The Histopathological Registry missed data about the histological type of BCC in 27 examinees.

Based on the results of histopathological analysis presented in Table 4, nodular type was the most commonly diagnosed (40%) (Figure 5), while together with mixed types (nodular-adenoid, nodular-adenoid-fibroblastic and mixed) it occurred in 49 examinees, followed by the adenoid (12%). The difference between the percentage of patients with

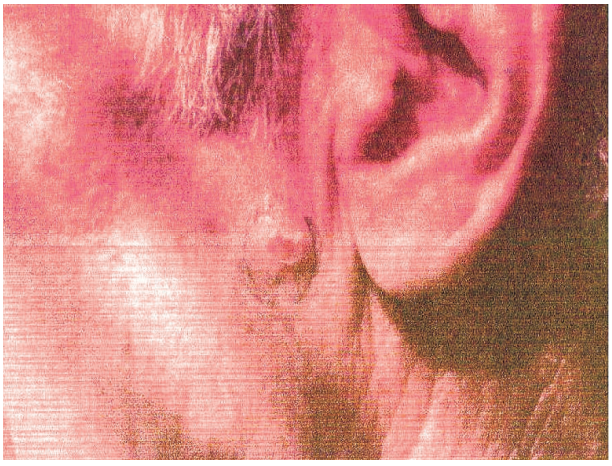

Figure 1. Basal cell carcinoma: nodular type

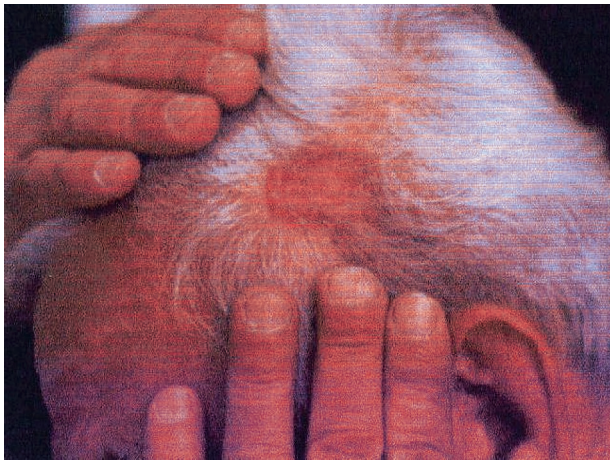

Figure 2. Basal cell carcinoma: noduloulcerative type

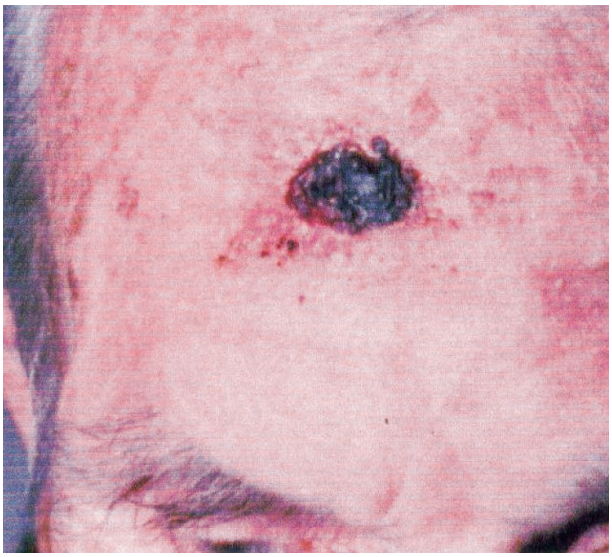

Figure 3. Basal cell carcinoma: ulcerative type

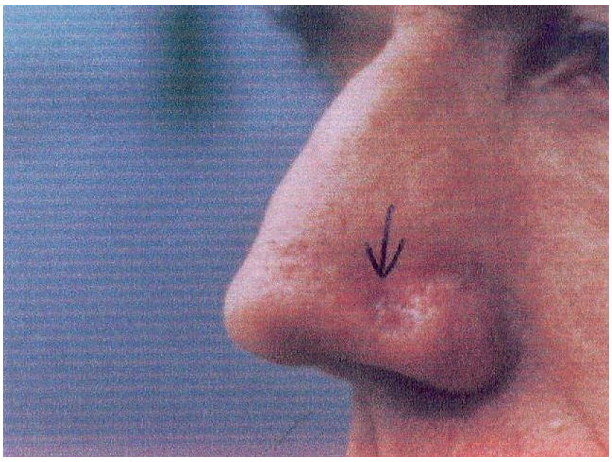

Figure 4. Basal cell carcinoma: ulcerosclerosis type

nodular versus adenoid type of BCCs was statistically significant (p<0.0001), contrary to all nonspecific types together (27%) which is on the borderline of statistical significance (p=0.05)

Tumor process was found on excision margins in 6% of patients (Table 4).

Discussion

This study included 58 men and 42 women selected by random sampling. The sex ratio was 1.4:1 in favour of men (p<0.05), which is in accordance with literature data showing a range of 1.1-1.4 : 1 in favour of men (32, 33, 34).

The average age of examinees was 66.6 ± 12.2 years (range 23 – 90 years), with similar data found in other studies, where the average age of patients with BCC ranged between 64.5 to 71 years (32, 33, 34, 35, 36).

The employment status was related to the age of the examined patients, but also with the altered demographic structure in the country: workers living in the country, or returned to the country after retirement (37). Taking into consideration the fact that most examinees lived in the country (p<0.001), whether as retired workers, farmers or housewives, and that they were engaged in agriculture, it is easy to assume that UV radiation played a significant role in the development of the disease. According to our results, BCC was most commonly (p<0.0001; 87%) located on continually sun-exposed areas (head including face and scalp, and neck), which is in agreement with literature data showing that BCC commonly affects the head and neck, with a prevalence between 85% and 56.9% (19, 36, 38). Martel (19) described BCC located on the head and neck in 85% of examinees (28% of which were on the nose), while Meneses and associates (36) found them in 74.5% of examinees. Artis and associates reported a lower prevalence (38): in their patients BCC was also most commonly found on the head and neck, but in around half of them (55.9%) on the trunk (33.9%), upper extremities (3.6%), and on lower extremities in 6.0%. According to the results of Dauden and associates (33), BCC was located on the face in 45.8% of patients, on the trunk in 29.3%, upper extremities in 19.5%, and on lower extremities in 4.7%. In our patients BCC was commonly located on the face (77%), and less

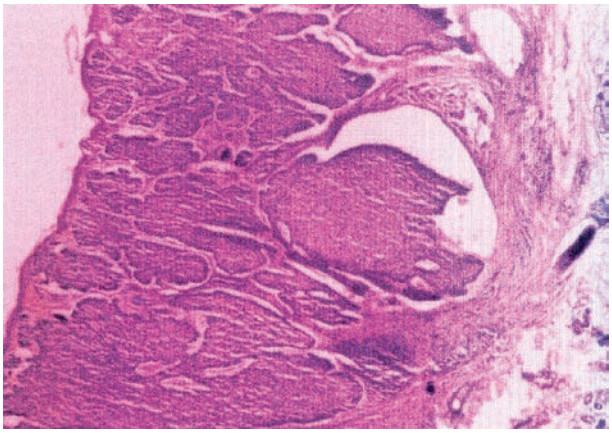

Figure 5. Basal cell carcinoma: histological presentation of the nodular (solid) type (HE staining x100)

Table 4. Clinical and histopathological types of basal cell carcinomas

Basall cell carcinoma	Number n=100
Clinical types	
Nodular	38
Nodulo-ulcerative	19
Ulcerative	5
Superficial	7
Pigmented	1
Ulcero-sclerotic	4
Morpheaform	1
Non specified	25
Histopathological subtypes	
Nodular (solid)	40
Adenoid	12
Solid adenoid	5
Fibroblastic	2
Solid adenoid fibroblastic	2
Superficial	7
Infiltrative	1
Morpheaform	1
Mixed	2
Pigmented	1
Non specified	27
Excision	
Total	72
Partial	6
Non-specified	22

commonly on the trunk (11%) and extremities (2%), probably due to exposure to UV radiation.

According to Abeldano and associates (39), BCCs located on the head and neck were caused by sun irradiation in 85 – 90% of cases, while BCCs on non-exposed regions are very rare and may point to another etiological mechanism. In 11% of our examinees with BCC on non-sun-exposed areas, we were not able to establish data on other etiological factors. Given the current hypothesis that reduced immune status caused by UV radiation at distant sites can be a BCC pathomechanism in places protected from the sun (40), this could mean that in these 11% of cases the role of UV radiation may not be completely excluded. Literature data show that BCCs may occur in atypical and unusual locations (40): on the vulva (41,42; in the axilla (43,44). BCC was found on the dorsal side of the hand in one of our patients, which is extremely rare, although this region is mostly exposed to the sun, which may be explained by low concentration of pilosebaceous units in that skin region (36). Apart from exposition to ultraviolet radiation, the prevalence of BCC also depends on skin types (1). Due to retrospective features of this study, we could not

completely process data concerning types of skin, in order to obtain adequate and conclusive statistical data.

There are four main clinical types of BCC: nodular, pigmented, superficial, and morpheaform (45). Some authors classify BCCs into 7 clinical types (46), others into 5 (47), or into 5 basic, 2 atypical, and 3 rare clinical types (48), or 10 types (49). None of the classifications coincide completely. Taking into account locations of BCCs in our patients, the most common registered clinical type was nodular (57%), with a significantly higher number of nodular BCCs without than with ulcerations ($p<0.01$). The clinical classification itself has little or no importance for the prognosis. However, the prognosis of basal cell carcinoma is clearly related to its size (1).

There are also differences among authors when the terminology of histological types is concerned (47, 48, 50, 51, 52, 53), but most of them described the following types: nodular, adenoid, superficial, keratotic, pigmented, morpheaform, infiltrative, cystic, metatypical, fibroepithelioma, and basosqamocellular carcinoma. There is also a classification of differentiated and non-differentiated types. The differentiation pathway is directed towards cutaneous adnexa (keratotic, cystic, adenoid), while non-differentiated includes the nodular type (46). It is particularly valuable to classify the histologic appearance, because of the existing relationship between histologic subtype and clinical behavior: aggressive histologic variants include the micronodular, infiltrative, morpheaform; basosquamous, and mixed subtypes; nodular and superficial subtypes are characterized with a less aggressive clinical course (52). In 2006, WHO published classification of skin tumors which recognizes 8 histological types of BCC: superficial, nodular, micronodular, infiltrating, fibroepithelial, basosquamous, keratotic and basal cell carcinoma with adnexal differentiation (53). There are still differences in the terminology of histological types (1). Considering the fact that in our patients nodular type of BCC (40%) was most commonly (significantly more often than the second, adenoid type, $p<0.0001$) diagnosed, it is in accordance with Meneses and associates who analyzed histopathological preparations in 269 patients with BCC, and found the nodular type in most cases (36). Rigell and associates (46) reported the nodular type of BCC in 60% of all histological subtypes, mostly located on the head and neck, but it may also be found on the trunk and extremities. Meneses and associates found that the next most commonly diagnosed were multifocal, superficial, and adenoid types, whereas morpheaform, metatypical and cystic were rather rare. None of our patients presented with metatypical (basosquamous) basal cell carcinoma. Interesting results were obtained by Aguilar Bernier and associates (21) who conducted a comparative epidemiological study of the differences in the prevalence of certain histological types of BCCs between Spaniards on the one hand, and the Europeans originating from northern and central Europe on the other hand, who were settled on the sunny Riviera, Spanish Costa del Sol. In both examined groups of inhabitants the most common type of BCC was superficial (20.4% and 28.2%), then infiltrative (20.8% and 19.6%), nodular (16.7% and 9.9%), undetermined (7.0% and 10.0%), and micronodular (0.9% and 0.4%). Such a high prevalence of superficial BCCs can be a result of patients' education. In our patients, the superficial type was diagnosed only in 7%.

In Australia, although still less common than the nodular type, compared with Europe, there are proportionately more superficial basal cell carcinomas, and in females the incidence is maximum in the 40–49 years age group (27). According to Raasch and associated, the superficial type of BCC accounts for 25%–26% of all BCCs in sun-exposed Australians, and for 15%–16% of all types in Europe: the most common are located on the trunk and extremities, excluding the population highly exposed to sun, who may have them on the face (27, 54).

Current therapy of BCC includes destructive and surgical procedures (55). Surgical excision is the gold standard for BCC: conventional, conducted in our patients, and Mohs micrographic surgery, which takes a significant place in the treatment of high-risk BCCs (56). When choosing therapeutic modalities, factors that increase the risk of recurrence and/or incidence of metastasis spread should be considered, such as: BCCs at high-risk sites (nasolabial fold, periocular and nose), BCCs greater than 2 cm in diameter, certain histological subtypes (morpheaform, infiltrative, micronodular, basosquamous), and recurrent BCCs (1). According to ANEAS (Agence Nationale d'Accreditation et Evaluation en Santé) (57) moderately risky locations for surgical excision

include the anterior part of the head, temples, cheeks, neck, chin and scalp, while high risk locations are the nose, ear, orbit and lips.

The excised area must be surrounded by healthy tissue to make the excision adequate (58, 59), highly affecting its outcome (56). In 6% of our patients a tumor process was found on the margins of excision. Santiago and associates found 90 (9.5%) incomplete excisions out of 947 BCC excisions. In 29 (32.2%) of these patients, recurrence was confirmed. The median recurrence was 12 months (range 1 – 57) (60). Depending on the location, size, margins of the tumor, previous treatment and histology, excision of BCC margins from 3 – 10mm may be rational in at least 95% of cases (61, 62). Thus, Rigell and associates used a margin of 4mm and adequately removed 98% of nonmorpheaform tumors less than 2cm in diameter (46). Dermoscopy of excised margins provides histologic confirmation of the complete excision in 98.5% of cases (63). It has been established that the risk for the development of new BCCs decreases with time: it is 11.6 in the first year, and 6.3 in the second (32). In cases where incomplete excision is performed on lateral margins only, it may be reasonable not to re-excise if the BCC is a primary tumor on a non-critical site and non-aggressive histology (1).

Conclusion

In our samle, basal cell carcinoma was more common in males than in females. Significantly more people with excised basal cell carcinoma lived in the country. An age-related increase in the number of patients with BCC has been established, and most patients with excised basal cell carcinoma belonged to the age group of 61 to 81 years. In most patients the tumor was located on the face, whereas clinically and histopathologically, nodular type was the most common.

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Bazocelularni karcinom: retrospektivna kliničko-histološka analiza 100 slučajeva na osnovu Histopatološkog registra Instituta za patologiju u Nišu

Sažetak

Uvod: Bazocelularni karcinom najčešći je maligni tumor kože. Tumorske ćelije potiču od pluripotentnih ćelija bazalnog sloja epiderma, spoljašnjeg omotača folikula dlake (eng. *outer root sheath of the hair follicle*), lojnih i znojnih žlezda.

Cilj: Cilj ispitivanja bio je da se analizom bolesnika sa bazocelularnim karcinomom kože utvrdi distribucija oboljenja prema polu, životnom dobu, profesiji, lokalizaciji, kliničkim oblicima i patohistološkim karakteristikama promena.

Materijal i metode: U ovoj retrospektivnoj studiji urađena je, na osnovu Histopatološkog registra Instituta za patologiju u Nišu, klinička obrada (demografski podaci, anamneza, klinička slika) i patohistološka analiza hirurški ekscidiranih tumora kod 100 osoba koje su izdvojene metodom slučajnog izbora iz grupe od 263 pacijenata, kod kojih je konsekutivno u periodu od petnaest meseci na osnovu patohistološkog nalaza, postavljena dijagnoza bazocelularnog karcinoma.

Rezultati i diskusija: Odnos polova (muškarci : žene) bio je 1,4 : 1 ($p<0,05$), što je u skladu sa podacima iz literature, po kojima se ovaj odnos kreće od 1,1–1,4 : 1 (muškarci : žene). Dve trećine obolelih bilo je starije od 60 godina. Prosečna starost iznosila je 66,6 ±12,2 godina (raspon 23–90 godina), a slični podaci nalaze se i u drugima studijama u kojima se prosečna starost osoba sa bazocelularnim karcinomom kože kretala u rasponu 64,5–71 godine. U skladu sa starosnom strukturom, 53 pacijenta bili su penzioneri (uglavnom poljoprivredni), 12 radnici, 14 zemljoradnici, 12 bez stalnog zaposlenja, 5 domaćice i 4 pacijenta bili su službenici. S obzirom na mesto stanovanja, 61% osoba je živelo na selu. Status zaposlenosti bio je u skladu sa godinama života, ali i u skladu sa izmenjenom strukturom našeg sela, tj. stanovanjem radnika na selu ili povratka u selo po završetku radnog veka. Kada se uzme u obzir da je značajna većina ispitanika živela na selu ($p<0,001$), bilo da su penzionisani radnici, poljoprivrednici ili domaćice i da su se bavili poljoprivredom, onda se može pretpostaviti značajna uloga izlaganja ultravioletnom zračenju u nastanku oboljenja: bazocelularni karcinom kože bio je češće lokalizovan na licu (77%) a ređe na trupu (11%) i ekstremitetima (2%). Nije bilo podataka o ekspoziciji x-zracima i hemikalijama (izuzev pesticida i insekticida), ožiljcima od opekotina i genodermatozama. U 87% slučajeva, bazocelularni

karcinom kože je značajno najčešće (p<0,0001) bio lokalizovan na mestima stalno izloženim suncu (glava, tj. lice i poglavina i vrat), što se slaže sa podacima iz literature, prema kojima se bazocelularni karcinom kože najčešće javlja na glavi i vratu, a prevalencija se kreće između 85% i 56,9%. Prema podacima iz literature, bazocelularni karcinom kože lokalizovan na glavi i vratu je u 85–90% slučajeva izazvan sunčanom radijacijom, a na foto-neeksponiranim regijama javlja se retko i može značiti prisustvo nekog drugog etiološkog mehanizma. Kod 11% naših ispitanika, kod kojih je lokalizacija bazocelularnog karcinoma kože bila na fotoneeksponiranim regijama, mi nismo mogli utvrditi podatke o drugim etiološkim faktorima. S obzirom na postojeću hipotezu da smanjeni imunonadzor izazvan ultravioletnom radijacijom na udaljenim mestima, može predstavljati patomehanizam nastanka bazocelularnog karcinoma kože na mestima zaštićenim od sunca, to bi moglo značiti da se i u ovih 11% slučajeva nije mogla u potpunosti isključiti uloga ultravioletnog zračenja.

U literaturi su objavljeni slučajevi bazocelularnog karcinoma kože sa atipičnim i neuobičajenim lokalizacijama – na vulvi i u aksili. Bazocelularni karcinom kože je registrovan na dorzalnoj strani šake kod jedne naše pacijentkinje, što se izuzetno retko viđa, iako je ova regija često izložena suncu, što bi se moglo objasniti malom koncentracijom pilosebacealnih jedinica na toj regiji kože.

Najčešći klinički oblik bio je nodularni (57%), a bili su dijagnostikovani i superficijalni (7%) ulcerozni (5%), ulcerosklerotični tip (4%), pigmentni (1%) i morfeaformni (1%). U 25% slučajeva, u Histopatološkom registru nisu postojali podaci na osnovu kojih bi se mogao tačno odrediti klinički tip bazocelularnog karcinoma kože. Pojedini autori klasifikuju bazocelularni karcinom kože u 7 kliničkih tipova, drugi u 5, ili u 5 osnovnih, 2 atipična i 3 ređa klinička tipa, ili u 10 tipova. Nijedna od podela se ne poklapa u potpunosti. S obzirom na lokalizaciju kod naših pacijenata, najčešće je bio registrovan nodularni klinički oblik pri čemu je značajno više bilo nodularnih bez ulceracije nego sa ulceracijom (p<0,01). Sama za sebe, klinička klasifikacija je od malog značaja za prognozu. Veličina lezije predstavlja faktor rizika koji utiče na prognozu.

S obzirom na lokalizaciju i kliničku sliku bazocelularnog karcinoma kože kod naših ispitanika, najčešće dijagnositikovan histološki tip bio je nodularni, što je u saglasnosti sa rezultatima u literaturi. Smatra se da nodularni histološki tip ovog karcinoma čini do 60% svih histoloških tipova, najčešće se lokalizuje u predelu glave i vrata, ali se može lokalizovati i na trupu i ekstremitetima. Na osnovu rezultata patohistološke analize u našem ispitivanju, pored nodularnog tipa (40%), bili su dijagnostikovani značajno ređe i adenoidni (12%) (p<0,0001), mešoviti tipovi (nodulo-adenoidni, nodulo-adenoidno-fibroblastični i mikstni) (9%), superficijalni (7%), fibroblastični (2%), infiltrativni (1%), pigmentni (1%) i morfeaformni (1%). U 25% slučajeva u Histopatološkom registru nisu postojali podaci na osnovu kojih bi se mogao tačno odrediti klinički tip bazocelularnog karcinoma kože.

Histološka klasifikacija je od velikog značaja s obzirom da histološka građa tumora utiče na njegov klinički tok: agresivni histološki suptipovi (mikronodularni, infiltrativni, morfeaformni; bazoskvamozni i mešoviti); manje agresivni histološki suptipovi (nodularni i superficijalni). I u terminologiji histoloških formi postoje razlike među autorima. Svetska zdravstvena organizacija je objavila klasifikaciju sa 8 histološki tipova: superficijalni, nodularni, mikronodularni, infiltrativni, fibroepitelijalni, bazoskvamozni, keratotični i bazocelularni karcinom sa adneksalnom diferencijacijom.

Terapija: Zlatni standard u terapiji bazocelularnog karcinoma kože jeste hirurška ekscizija: konvecionalna koja je sprovedena u ovom radu i Mohsova mikrografska koja ima značajno mesto u lečenju visokorizičnih bazocelularnih karcinoma kože. Mesto ekscizije mora biti okruženo zdravim tkivom da bi ekscizija bila adekvatna, što određuje njen uspeh. Kod 6% naših bolesnika nađen je tumorski proces na ivicama ekscizije. Santiago i saradnici su od 947 bazocelularnih karcinom kože koje su ekcidirali nekompletnu eksciziju našli kod 90 (9,5%) bolesnika. Kod 29 (32,2%) ovih bolesnika potvrđen je recidiv. Prosečno trajanje remisije je iznosilo 12 meseci (raspon od 1 do 57 meseci). Zavisno od mesta, veličine, ivica tumora, prethodnog tretmana i histologije, ekscizija margina bazocelularnog karcinom kože od 3–10 mm, može biti racionalna u najmanje 95% slučajeva. Tako su Rigel i saradnici, sa marginom od 4 mm, adekvatno uklonili 98% nemorfeaformnih tumora manjih od 2 cm u prečniku. Dermoskopskom detekcijom ekscizionih ivica može se dobiti histološka potvrda kompletne ekscizije u

98,5% slučajeva. Utvrđeno je da rizik od razvoja novih bazocelularnih karcinom kože vremenom opada: u prvoj godini iznosi 11,6, u drugoj godini iznosi 6,3. U slučajevima da se inkompletna ekcizija odnosi samo na lateralne ivice tumorskog tkiva, a da se radi o primarnom tumoru koji se ne nalazi na kritičnom mestu i nema agresivnu histološku građu, odluka da se ne radi reekcizija može biti opravdana.
Zaključak: Bazocellularni karcinom je bio značajno češći kod osoba muškog pola. Značajno veći broj osoba sa ekscidiranim bazocelularnim karcinomom živeo je na selu. Utvrđen je značajan porast broja obolelih sa starošću i najveći broj osoba sa ekscidiranim bazocelularnim karcinomom pripadao je starosnoj kategoriji od 61. do 81. godine života. Kod najvećeg broja osoba tumor je bio lokalizovan na koži lica, a najčešći klinički i patohistološki dijagnostikovan tip bio je nodularni tip.

Ključne reči

Bazocelularni karconom + dijagnoza + klasifikacija + etiologija + epidemiologija; Neoplazme kože + hirurgija; Starosni faktori; Neoplazme po mestu nastanka; Sunčeva svetlost

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Granuloma faciale – a difficult diagnosis? – A case report

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VERSITA

Abstract

Granuloma faciale is an uncommon inflammatory skin disorder clinically characterized by single or multiple, reddish-brown nodules or plaques primarily occurring on the face of middle-aged men. Occasionally, extra-facial involvement has been reported, usually on sun-exposed areas. Although the etiology is somewhat unclear, granuloma faciale is considered a localized form of chronic leukocytoclastic vasculitis with a prominent eosinophilic infiltrate and fibrosis in the later stages of the disease. Histological examination of lesions reveals a dense polymorphous inflammatory infiltrate that consists mainly of eosinophils and neutrophils separated from the epidermis by a narrow band zone with normal collagen, deprived of cells. Leukocytoclastic vasculitis is often seen. Clinical diagnosis is suspected in few cases, so definite diagnosis of granuloma faciale requires a biopsy. The disease is notoriously resistant to many therapies and often tends to relapse after treatment is discontinued.

We present a female patient with granuloma faciale on the back and on the tip of the nose, misdiagnosed clinically as basall cell carcinoma and granuloma annulare. Her original histological diagnosis, made by a pathologist, was pyogenic granuloma. After revision of histologic findings of the biopsy specimens, granuloma faciale was diagnosed by a dermatopathologist. The treatment with cryotherapy and topical steroids was unsuccessful. Improvement of lesions was observed after use of tacrolimus 0.1% ointment, but lesion recurred after discontinuation of treatment.

Key words

Granuloma + diagnosis; Skin Neoplasms; Cryosurgery; Tacrolimus; Administration, Topical; Histology

Granuloma faciale (GF) or *granuloma faciale eosinophilicum* is a rare chronic inflammatory disease clinically characterized by asymptomatic cutaneous reddish brown to violaceous nodules and plaques occurring primarily on the face, with occasional extrafacial involvement. The term granuloma faciale was originally described by Wigley in 1945 (1) as eosinophilic granuloma of the skin, and was defined more precisely by Lever and Leeper (2), whereas Pinkus recommended the present term in 1952 (3). Although the etiology is somewhat unclear, GF is considered a localized form of chronic leukocytoclastic vasculitis with a prominent eosinophilic infiltrate and fibrosis in the later stages of the disease. Granuloma faciale is limited to the skin, without any systemic manifestations. The disease is found in both sexes, at any age, but it usually affects middle-aged men (4). Clinically, GF presents with reddish-brown to violaceous plaques on the face, often with follicular accentuation and superficial telangiectasia. The sites of predilection are sun-exposed areas such as the sides and tip of the nose, the preauricular area, the cheeks, forehead and the helix of the ear. Definite diagnosis of GF requires clinically consistent lesions and a confirming biopsy. Histological examination of the lesions reveals a dense polymorphous inflammatory infiltrate that consists of eosinophils, neutrophils, lymphocytes, histiocytes, plasma cells, fibroblasts in the upper two-thirds of the dermis or even to subcutis, which is separated from the epidermis and pilosebaceous units by a narrow zone deprived of cells (Grenz zone) (5). Leukocytoclastic vasculitis