REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Emerging concepts and latest advances regarding the etiopathogenesis, morphology and immunophenotype of basal cell carcinoma

MARIANA COSTACHE[1,2)], TIBERIU AUGUSTIN GEORGESCU[1,2)], ANA MARIA OPROIU[2,3)], DIANA COSTACHE[2)], ALEXANDRU NAIE[2)], MARIA SAJIN[1,2)], ADRIANA ELENA NICA[2,4)]

[1)]*Department of Pathology, University Emergency Hospital, Bucharest, Romania*
[2)]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3)]*Department of Plastic Surgery, University Emergency Hospital, Bucharest, Romania*
[4)]*Department of Anesthesiology and Intensive Care, University Emergency Hospital, Bucharest, Romania*

Abstract

Basal cell carcinoma (BCC) represents the most common skin malignancy, which has been linked over time to multifactorial causes. It usually occurs on sun-exposed areas in people with fair skin and with predilection for men. BCC usually affects elderly patients and has an extremely wide range of histological subtypes, which can present clinically under different variants, some with really challenging differentials. Although BCC may occur in familial settings, such as nevoid BCC syndrome, Rombo or Bazex–Dupré–Christol syndromes, nonsyndromic multiple BCCs have also been described in the scientific literature. In this review, we discuss in detail the latest scientific concepts regarding BCC, its etiology, pathogenesis, genetic bases of disease, morphology and immunophenotype, as well as the currently known genetic syndromes, which may lead to development of multiple BCCs, especially in young adults.

Keywords: basal cell carcinoma, Rombo syndrome, Bazex syndrome, nevoid basal cell syndrome.

Introduction

Basal cell carcinoma (BCC) is the most frequent malignant tumor encountered in dermatopathology, which occurs with progressively increasing rate not only in Romania, but also in all other countries around the Globe. In the United States, BCC constitutes over one-third of all cancers, affecting one-fifth of all Americans and being the most common non-melanoma skin cancer, with over one million new patients being treated every year, as reported in studies by Bath-Hextall *et al.* and Rogers *et al.* [1, 2]. The incidence of BCC is more than four times higher than that of squamous cell carcinoma (SCC) and 20 times higher than that of melanoma. Although it increases by 3–10% each year, the incidence of BCC features important regional variation. Epidemiological data reveals marginally lower numbers in Northern Europe, compared to a considerably higher incidence in Australia. Statistical analyses involving the nationality and gender of affected populations, demonstrated that BCC occurs more frequently in men than in women and rarely affects black people. In Oriental population, BCC is usually pigmented. The risk for Caucasian men have a lifetime risk of up to 39% to develop BCC, while for women, the values range between 23% and 28%. Latest epidemiological studies reveal that women and adults younger than 40 years tend to be more frequently affected with each passing year [1, 3–5].

Etiopathogenesis

The exact histogenesis of BCC has not been completely elucidated, but it has been hypothesized that the tumor arises from a epithelial stem cells located at interfollicular level, within the hair follicle root sheath or sweat duct system and have many similarities with follicular matrix cells, both immunohistochemically and ultrastructurally [6–8].

The sudden rise in incidence rates for BCC could be related to environmental changes, lifestyle and behavioral risk factors. BCC mainly affects photoexposed regions and in approximately 80% of cases, it develops in the head and neck region, mainly on the skin of cheeks and nose [9]. Since the trunk and limbs are not as photoexposed as the face, those regions are less frequently affected by BCC. Even less frequently, perianal and genital areas may develop BCC [10]. Cumulative and intermittent exposure to ultraviolet (UV) radiation (especially UVB rays with wavelengths of 290–320 mm), as well as the inadequate protection provided by fair skin results in various mutations within the epithelial cells, which may eventually lead to the development of BCC [11, 12]. Predisposing factors for BCC include several genotypic, phenotypic, and environmental causes. Predisposition for BCC is not only genetically correlated, but also increased by factors related to behavior and environment, such as frequent sunburns, especially in patients with skin phenotype I and II, green or blue eyes, blonde or red hair. Other skin

conditions like albinism, actinic keratosis, xeroderma pigmentosum and lentigines also play an important role in the pathogenesis of BCC [13, 14]. A high degree of freckling also correlates with an increased incidence of BCC, while Southern European ancestry has a protective effect. Not exceptionally, BCC may occur in non-sun-exposed regions, such as the axilla or pubic region, where the etiopathogenic role of UV exposure could not be incriminated. Moreover, BCC has also been described in hairless regions such as the vulvar semimucosa, of the nipple, resulting in disagreements concerning its histogenetic origin.

Genetic basis of disease

Similar to melanoma and SCC, the development of BCC is highly influenced by exposure to UV radiation, which is responsible for the increased frequency of specific mutations described in this tumor [15, 16]. However, besides these "UV signature" genetic alterations, sporadic BCC can occur in association with other mutations as well.

Genetic studies in patients with Gorlin–Goltz syndrome (nevoid BCC syndrome) have demonstrated germline mutations in the *PTCH1* gene found on chromosome 9q22.3, resulting in an error of signaling in hedgehog (HH) pathway, which makes the patient susceptible to development of BCC, as well as other developmental defects. *PTCH1* is a tumor suppressor gene, which encodes a transmembrane protein that works as receptor for sonic hedgehog (SHH) ligands. Molecular somatic mutations in the *PTCH1* gene and other genes encoding proteins of the HH pathway have also been detected in sporadic BCC [17–20]. This signaling pathway has provided the oncologists with new therapy opportunities.

Although less important than *PTCH1* gene, mutation of *p53* tumor suppressor gene represents another pathway involved in the tumorigenesis of BCC [21]. *P53* is known to be responsible for the integrity of the genome and can also regulate the cell cycle [22], but in some human cancers, such as SCC, it can feature multiple mutations. More than 50% of BCCs present mutations in *p53* gene. Recent research demonstrated that UVB exposure induces deoxyribonucleic acid (DNA) damage at mutation hotspots in *p53*, which in the scientific literature have been referred to as "UV signature".

Morphology and immunophenotype

Most authors agree that BCC can be divided in five clinical subtypes, some of which were named due to their histopathological architecture: nodular/ulcerative variant (45–60%), diffuse infiltrative or morpheaform variant (4–17%), superficial or multifocal variant (15–35%), pigmented variant (1–7%) and fibroepithelioma of Pinkus. BCC presenting as a linear pigmented lesion was first described by Lewis, in 1989 [23]. Since then, this variant was subsequently reported by many other authors who consider it a distinct entity, especially due to its particular clinical and histopathological characteristics.

Histologically, most BCCs are composed of small basaloid cells, with scant blue-grey cytoplasm and dark ovoid nuclei haphazardly arranged in lobules protruding from the overlying epidermis. The lobules usually feature peripheral palisading, with the long axes of the cells aligned and perpendicular to the interface between the basaloid cell lobules and the stroma. Key morphological features present in most BCCs include mucinous stroma and tumor retraction artifact, but even those may be absent in some cases. BCC has an extremely wide range of histological subtypes, some of which are very rare and/or are characterized by the presence of particularly distinctive features.

Nodular BCC

Nodular BCC is the most frequent subtype, representing approximately 60–80% of all BCCs, which usually emerges on the skin of the head. Clinically, it appears as an elevated, exophytic pearl-shaped nodule with overlying telangiectasias and rolled borders. It usually begins as a slow-growing papule that will often ulcerate and bleed. The latter may mislead male patients to dismiss the neoplasm as a cut while shaving. Histologically, nodular BCC is composed of large basaloid lobules of variable size and shape, forming a relatively well-circumscribed mass. The lobules may be solid or show central cystic dilatation (nodulocystic BCC). The stroma between the lobules varies in quality and quantity, usually being loose and mucinous and shows a characteristic retraction artifact around the tumor lobules. The stroma in BCC is almost never fibrous, which is a main differential diagnosis clue. The separation of the tumor lobules from their associated stroma (also known as artefactual clefting) is partly a fixation artifact due to mucin shrinkage during tissue processing, but also related to basement membrane abnormalities of adhesion as well as reduced expression of bullous pemphigoid antigen and diminished number of hemidesmosomes and anchoring fibrils. The stroma of BCC may also contain amyloid deposits, especially in solid, adenoid, and cystic histological subtypes [24]. Subsequently, nodular BCC may develop into ulcerative or cystic pattern. Immunohistochemically, almost all BCCs are positive for cytokeratin 5/6 (CK5/6), Ber-EP4, p63, p53, B-cell lymphoma 2 (Bcl-2), cluster of differentiation 10 (CD10) and actin.

Adenoid BCC may present as a reticulate, cribriform or pseudoglandular proliferation of basaloid cells with an almost pure mucinous stroma as well as mucin deposits within the basaloid aggregates, which maintain conspicuous peripheral palisading. Adenoid cystic carcinoma, which is a common malignant neoplasm of the salivary gland, should always be included in the differential diagnosis of BCC.

Diffuse variant of BCC

Diffuse variant of BCC represents the prototype of micronodular, morpheaform or infiltrative BCC.

Micronodular BCC

Micronodular BCC, a particular variant of BCC, which is more commonly localized on the back of the trunk, is composed of multiple small-sized and relatively uniform basaloid nests with limited peripheral palisading. The absence of a retraction artifact is typical of this variant, which translates to a high local recurrence rate. Micronodular BCC seldom ulcerates, but often features a

diffusely infiltrative pattern, with extension into the subcutaneous tissue. Brisk mitotic activity and apoptosis help distinguish this variant from trichoepithelioma.

Infiltrative BCC and morpheaform BCC

Infiltrative BCC and morpheaform (sclerosing) BCC clinically present as firm, scar-like plaques and should be considered in the presentation of a new scar without previous trauma in that specific area. Histologically, both subtypes are composed of thin strands of basaloid cells, featuring jagged border and limited or no peripheral palisading. In contrast to the infiltrative variant, which features characteristic loose and mucinous stroma, the morpheaform variant shows dense and sclerotic stroma, which presents clinically as an infiltrative plaque with slightly shining surface and poorly-defined borders. Both variants frequently feature extensive spread and perineural invasion [25]. The highly fibroblastic stroma of morpheaform/infiltrating BCC can pose differential diagnosis problems with desmoplastic trichoepithelioma. Immunohistochemical (IHC) distinction involves CK20, which is completely negative in BCC but should reveal positive Merkel cells in trichoepithelioma as well as androgen receptor, which should be positive in BCC but negative in trichoepithelioma. Moreover, the epithelial component in BCC shows diffuse immunopositivity for CD10, while the stromal compartment is completely negative. In trichoepithelioma or trichoblastoma (which is more of a differential for the nodular variant rather than the infiltrative form), CD10 shows intense positivity in the stroma around the tumor and is usually completely negative or weakly positive in the epithelial compartment.

Metatypical BCC

Metatypical (basosquamous) BCC represents an intermediate typology between classic BCC and SCC, containing multiple foci of neoplastic squamous differentiation. Usually, it has an infiltrative growth pattern and features increased proliferation rates, being associated with worse outcome and elevated risk for distant metastasis.

Pigmented BCC

Pigmented BCC is more frequent in darkly pigmented races and can contain melanin within dendritic melanocytes located among tumor nests, or within stromal macrophages. Sometimes, hemosiderin deposits and moderate inflammatory infiltrate may also be evident. Pigmentation can vary from dark tan to black and may accompany various histological subtypes of BCC. The only significance of pigmented BCC is the clinical confusion with melanoma.

Superficial BCC

Superficial (multifocal) BCC clinically presents as a thin, pink plaque, papule, or macule with a pink, pearly border that is most commonly seen on the chest, back, or extremities. Due to their lack of marked color variation, compared to normal skin, BCCs might elude early detection and lead to increased morbidity. However, Adler *et al.* proposed a new method for subclinical entities to be identified. If the lesion is stroked with a wipe, which was previously soaked in 70% isopropyl alcohol, then the lesion will turn bright pink. Moreover, upon dermoscopic examination, the tumor vasculature will become more easily identifiable [26]. This novel clinical sign described by Adler *et al.*, in 2017, is neither diagnostic nor pathognomonic, but it improves early detection of superficial BCC. Microscopically, the tumor is composed of apparently isolated small buds of basaloid tumor cells extending from the lower margin of the epidermis. Superficial BCC may feature areas of regression, presented as pale sections with fibrosis.

Pleomorphic BCC

Pleomorphic (giant cell) BCC is an uncommon subtype of BCC characterized by the presence of giant cells, which feature cytoplasmic changes in the form of inclusions, which may be either eosinophilic or basophilic. Rarely, one can also find intranuclear invaginations of the cytoplasm. Cellular pleomorphism, mitotic activity and apoptosis does not appear to influence tumor behavior.

Clear cell BCC

Clear cell BCC shows either focal or extensive clear cell change, without affecting peripheral palisading. This may be due to accumulation of glycogen, lipids, or may represent a degenerative phenomenon. Some studies have described the presence of Periodic Acid–Schiff (PAS)-positive granules within the cytoplasm of the cells [27, 28], while other authors have contradicted this theory [29, 30]. Histochemical studies have revealed that cytoplasm clarity is not due to the presence of intracellular mucin. However, mucinous material has been detected within the stroma [27, 29, 31].

Signet ring cell BCC

Signet ring cell BCC is microscopically heterogeneous, being composed of two distinct elements: one that resembles typical BCC and another composed of eosinophilic cells with plasmacytoid differentiation, the latter lacking specific peripheral palisading. Throughout the plasmacytoid component, scattered signet ring cells are always present. Ultrastructural studies have shown that vacuoles from these cells are actually represented by intermediate keratin filaments. IHC studies have shown that this tumor features myoepithelial differentiation, since it shows immunoreactivity for S-100, glial fibrillary acidic protein (GFAP) and smooth muscle actin (SMA) [32–34]. This IHC pattern may also be suggestive for a cutaneous myoepithelioma, which is the main differential diagnosis for this histological subtype of BCC [35].

Granular BCC

Granular BCC is a rare histological variant of BCC, which has not been reported more than 15 times to date [36]. Microscopically, at least some, if not all neoplastic cells show abundant eosinophilic cytoplasm with conspicuous granularity. Ultrastructural examination demonstrated that the cytoplasmic granules seen in optical microscopy are lysosome-like cisterns featuring electronodense bodies of approximately 0.3 μm [37–41]. Sometimes, pustuloovoid intracytoplasmic inclusions morphologically similar to Milan bodies seen in Abrikossoff tumor may also be identified in granular BCCs [37]. The pathophysiology of granular cell BCC is considered to be related to clear

cell BCC, being the consequence of a degenerative intracellular process. This variant has no clinical significance, behaves biologically similar to typical BCC and can be cured by complete surgical excision. Immunohistochemically, granular cell BCC shows immunopositivity for both high-molecular-weight and low-molecular-weight cytokeratins, AE1/AE3, Ber-EP4, p53, p16, D2-40 and Bcl-2 [42–44]. Immunostaining for CD68 may show focal expression limited to the cells with intracytoplasmic granules [44].

Infundibulocystic BCC

Infundibulocystic BCC is a newly described and extremely unusual form of BCC, which presents as an intradermal proliferation composed of many anastomosing epithelial cords and strands of basaloid cells with peripheral palisading and scant stroma. The tumor features several small infundibular cysts demarcated by basaloid cells with scant basophilic cytoplasm forming focal bud-like structures. This subtype usually appears as a solitary, dome-shaped tumor in the preauricular region of elderly patients and was previously described as BCC with follicular differentiation [45].

Metaplastic BCC

Metaplastic (sarcomatoid) BCC is an extremely rare histological subtype of BCC featuring stromal malignant metaplastic features (carcinosarcoma). Scientific data on the prognosis of this particular subtype is somehow contradictory. The sarcomatoid component can express diffuse immunopositivity for pan-CK AE1/AE3, CK5/6, CAM 5.2, p63 and D2-40 [46].

BCC with matrical differentiation

BCC with matrical differentiation (shadow cell BCC) is an exceedingly rare variant of BCC with only about 30 cases documented to date, mainly as isolated reports [47]. Microscopically, it is characterized by basaloid lobules containing central shadow cell nests that are typically seen in pilomatrixoma. The transition from basaloid cells to shadow cells is rather abrupt. The shadow cells are indicative of differentiation toward the pilar matrix, which was confirmed by electron microscopy [48]. Rare neoplasms may exhibit atypia in the matrical areas. Immunohistochemically, Ber-EP4 labels follicular germinative cells and is markedly reduced or negative in matrical areas, while β-catenin shows a reversed staining pattern. The BCC component lacks immunoreactivity for epithelial membrane antigen (EMA), however some matrical or supramatrical cells may exhibit focal positivity. Based on a clinicopathologic study of 22 cases, Kyrpychova *et al.* concluded that this subtype of BCC may feature various mutations, including: tumor protein 53 (*TP53*), Erb-B2 receptor tyrosine kinase 4 (*ERBB4*), *KIT*, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), *SMAD4*, catenin beta 1 (*CTNNB1*) and *PTCH1* genes, which may vary between the two elements [47].

Keloidal BCC

Keloidal BCC is not quite as rare as reported. Initially described by Requena *et al.* [49], in 1996, this histological subtype is characterized by the deposition of type I collagen (the same as in keloids), as thick, sclerotic bundles condensing the tumor stroma. This keloidal change is not a distinctive clinicopathological entity, but can accompany various histological subtypes of BCC and is frequently associated with morpheic features, ulceration and necrosis [50].

BCC with neuroid-type nuclear palisading

BCC with neuroid-type nuclear palisading is an exceptionally rare variant of BCC with very few case reports described in the scientific literature. The first case series of this histological subtype was published by Kadono *et al.*, in 1998 [51]. In addition to peripheral palisading characteristic for conventional BCC, the tumor features rather small and tightly packed tumor cells, uniformly arranged in parallel rows to form neuroid patterns. This particular arrangement of nuclei is a highly specific characteristic for tumors with neural differentiation, such as schwannoma or palisading encapsulated neuroma, but may also be seen in leiomyomas or palisading cutaneous fibrous histiocytoma [52, 53].

Fibroepithelioma of Pinkus

Fibroepithelioma of Pinkus (FeP) was regarded for many years as a subtype of BCC. However, recent scientific research studies have hypothesized that it might be a histological variant of trichoblastoma. Modern dermoscopic and IHC studies have established that FeP shares characteristics of both trichoblastoma and BCC. From a clinical standpoint, FeP may mimic a fibroepithelial polyp, pedunculated fibroma, seborrheic keratosis or an intradermal nevus. It appears as a stuck-on or pedunculated lesion with pale pink surface and firm or elastic consistency [54–56]. It may be pigmented [56–58] and it is usually solitary, but patients may present with multiple lesions, especially if they have had radiotherapy. The most frequent localization is the trunk, but it can also involve the anterior trunk, head and neck area as well as the lower limbs. The microscopic aspect is, as Pinkus described it, "peculiar and unmistakable". The tumor is composed of thin strands of basaloid epithelial cells, two to three cells thick, projecting downward from the epidermis, in a fenestrated pattern. From a three-dimensional viewpoint, FeP looks like a honeycomb or sponge comprised of thin intertwining trabeculae which demarcate stromal grooves [59]. Immunostaining is not particularly useful for diagnosis because histology is pretty distinctive, obviating the need for additional confirmation. FeP features a low Ki-67 proliferation index and reduced expression of p53, with slightly higher values within BCC-like nodular areas. Most cases are diffusely positive for Bcl-2 and immunostaining for CK20 will reveal Merkel cells. Immunostaining for androgen receptors will be positive in approximately four out of five of cases, with increased positivity within the anastomosing trabeculae than in the basophilic nubs, where they may be completely absent [60].

Genetic syndromes involving BCC

Nevoid BCC syndrome

Nevoid BCC syndrome (Gorlin–Goltz syndrome) is an autosomal dominant inherited disorder which equally affects both males and females and is characterized by

an increased number of BCCs affecting young patients, odontogenic keratocysts of the mandible and the maxilla, musculoskeletal defects, intracranial calcification and dyskeratotic pits of the palms and soles [61].

Bazex–Dupré–Christol syndrome

Bazex–Dupré–Christol syndrome also known as "follicular atrophoderma and basal cell carcinomas" is an extremely rare X-linked dominant genodermatosis of the hair follicle characterized by follicular artrophoderma, several BCCs, congenital hypotrichosis, multiple milia predominating on the face, and hypohidrosis, either generalized or confined to the face. It was first described by Bazex *et al.*, in 1964 [62] and has a prevalence of less than 1/10 000 000, with most cases reported in European male patients. BCCs develop early, during the second or third decade of life, although not as early as in Gorlin–Goltz syndrome.

Rombo syndrome

Rombo syndrome is a very rare autosomal dominant disorder, similar to Bazex–Dupré–Christol syndrome, initially described in 1981, by Michaëlsson *et al.*, which does not feature follicular artophoderma nor hypohidrosis [63]. Due to environmental factors, such as recreational sunlight exposure, the onset age may vary from individual to individual. However, most patients develop syndromic BCC after the age of 35 years. Clinically, individuals present with vermiculate atrophoderma of the face and sun-exposed areas, hypotrichosis with loss of eyelashes, milia-like papules, telangiectasias, cyanosis due to peripheral vasodilatation and multiple BCCs and/or trichoepitheliomas. Upon microscopic examination, nonspecific findings may be observed: some involving the distribution of elastin, which may be aberrant in the upper dermis or may be completely absent, others concerning the distribution of hair follicles, which may show some degree of atrophy. Dilated dermal vessels and milia may also be present.

To our knowledge, only eight patients with Rombo syndrome have been identified to date [64].

Clinical behavior

BCC should be in the differential for any new pink, pearly papule located on the trunk or in the head and neck region. In evolution, papules will eventually ulcerate and bleed. Medical history could assist in excluding acute lesions, such as acneiform papules, as patients frequently describe a never-healing or sporadically bleeding lesion manifesting for several weeks to months.

BCC rarely metastasizes, but it can produce major regional destruction when it is not properly diagnosed and treated. It is usually slow growing, can be cured by complete surgical excision and has good overall outcome [65, 66]. However, in rare cases, BCC may exhibit aggressive behavior, with multiple local recurrences or by developing distant metastases.

Although they are rarely the cause of death, multiple and recurrent BCCs severely affect the quality of life and their therapeutic management causes major load on the health care system [67].

The best treatment for BCC, regardless of histological subtype, is prevention with suitable protection from UV light exposure.

Conclusions

In Romania, or European countries in general, there is no nationwide registry surveillance system for BCC. Data is almost exclusively collected from population-based cancer registries, and because of this, epidemiological predictions are established based on limited information from specific states and regions. This may lead to over or underestimation of epidemiological data. Overall, we expect an exponential increase in the number of patients presenting with BCC over the coming years. Due to population growth and improvement in life expectancy, more and more resources will be necessary, which will cause a severe burden on the health care system. It is mandatory that we take into consideration the impending health and economic matters now and plan for the future. For this reason and due to the wide range of histological subtypes and variable clinical presentation, we highlight the importance of careful immunohistopathological examination for establishing the correct diagnosis of BCC.

Conflict of interests

The authors declare that they have no conflict of interests.

Compliance with ethical standards

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

References

[1] Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer, 2007, 121(9):2105–2108.
[2] Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, Coldiron BM. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol, 2010, 146(3):283–287.
[3] Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol, 2012, 166(5):1069–1080.
[4] Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjær SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978–2007: rapid incidence increase among young Danish women. Int J Cancer, 2010, 127(9):2190–2198.
[5] Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL, Roenigk RK. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA, 2005, 294(6):681–690.
[6] Wang GY, Wang J, Mancianti ML, Epstein EH Jr. Basal cell carcinomas arise from hair follicle stem cells in Ptch1(+/-) mice. Cancer Cell, 2011, 19(1):114–124.
[7] 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.
[8] Youssef KK, Van Keymeulen A, Lapouge G, Beck B, Michaux C, Achouri Y, Sotiropoulou PA, Blanpain C. Identification of the cell lineage at the origin of basal cell carcinoma. Nat Cell Biol, 2010, 12(3):299–305.
[9] Asilian A, Tamizifar B. Aggressive and neglected basal cell carcinoma. Dermatol Surg, 2005, 31(11 Pt 1):1468–1471.
[10] Mulvany NJ, Allen DG. Differentiated intraepithelial neoplasia of the vulva. Int J Gynecol Pathol, 2008, 27(1):125–135.
[11] Naumann IC, Cordes SR. Giant basal cell carcinoma of the forehead with extensive intracranial involvement. Ann Otol Rhinol Laryngol, 2007, 116(9):663–666.

[12] Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer – the role of sunlight. Adv Exp Med Biol, 2008, 624:89–103.
[13] Richmond-Sinclair NM, Pandeya N, Williams GM, Neale RE, van der Pols JC, Green AC. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study. Int J Cancer, 2010, 127(11): 2622–2629.
[14] Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med, 2005, 353(21):2262–2269.
[15] Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van't Veer L, Vincent-Salomon A, Waddell N, Yates LR; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. Nature, 2013, 500(7463):415–421.
[16] Jayaraman SS, Rayhan DJ, Hazany S, Kolodney MS. Mutational landscape of basal cell carcinomas by whole-exome sequencing. J Invest Dermatol, 2014, 134(1):213–220.
[17] Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. Mod Pathol, 2006, 19(Suppl 2):S127–S147.
[18] Lacour JP. Carcinogenesis of basal cell carcinomas: genetics and molecular mechanisms. Br J Dermatol, 2002, 146(Suppl 61): 17–19.
[19] LoRusso PM, Rudin CM, Reddy JC, Tibes R, Weiss GJ, Borad MJ, Hann CL, Brahmer JR, Chang I, Darbonne WC, Graham RA, Zerivitz KL, Low JA, Von Hoff DD. Phase I trial of hedgehog pathway inhibitor Vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. Clin Cancer Res, 2011, 17(8):2502–2511.
[20] Daya-Grosjean L, Couvé-Privat S. Sonic hedgehog signaling in basal cell carcinomas. Cancer Lett, 2005, 225(2):181–192.
[21] van der Riet P, Karp D, Farmer E, Wei Q, Grossman L, Tokino K, Ruppert JM, Sidransky D. Progression of basal cell carcinoma through loss of chromosome 9q and inactivation of a single p53 allele. Cancer Res, 1994, 54(1):25–27.
[22] Bieging KT, Mello SS, Attardi LD. Unravelling mechanisms of p53-mediated tumour suppression. Nat Rev Cancer, 2014, 14(5):359–370.
[23] Lewis JE. Liner basal cell epithelioma. Int J Dermatol, 1989, 28(10):682–684.
[24] Cox NH, Nicoll JJ, Popple AW. Amyloid deposition in basal cell carcinoma: a cause of apparent lack of sensitivity to radiotherapy. Clin Exp Dermatol, 2001, 26(6):499–500.
[25] Nadiminti U, Rakkhit T, Washington C. Morpheaform basal cell carcinoma in African Americans. Dermatol Surg, 2004, 30(12 Pt 2):1550–1552.
[26] Adler NR, Pan Y, Kelly JW. A novel clinical sign to aid in the diagnosis of superficial basal cell carcinoma. J Am Acad Dermatol, 2017, 77(6):e155–e156.
[27] Barr RJ, Williamson C. Clear-cell basal cell carcinoma. Arch Dermatol, 1984, 120:A1086.
[28] Barnadas MA, Freeman RG. Clear cell basal cell epithelioma: light and electron microscopic study of an unusual variant. J Cutan Pathol, 1988, 15(1):1–7.
[29] Oliver GF, Winkelmann RK. Clear-cell, basal cell carcinoma: histopathological, histochemical and electron microscopic findings. J Cutan Pathol, 1988, 15(6):404–408.
[30] Starink TM, Blomjous CEM, Stoof TJ, van der Linden JC. Clear cell basal cell carcinoma. Histopathology, 1990, 17(5): 401–405.
[31] Barr RJ, Alpern KS, Santa Cruz DJ, Fretzin DF. Clear cell basal cell carcinoma: an unusual degenerative variant. J Cutan Pathol, 1993, 20(4):308–316.
[32] Michal M, Miettinen M. Myoepitheliomas of the skin and soft tissues. Report of 12 cases. Virchows Arch, 1999, 434(5): 393–400.
[33] Alós L, Cardesa A, Bombí JA, Mallofré C, Cuchi A, Traserra J. Myoepithelial tumors of salivary glands: a clinicopathologic, immunohistochemical, ultrastructural, and flow-cytometric study. Semin Diagn Pathol, 1996, 13(2):138–147.
[34] Kutzner H, Mentzel T, Kaddu S, Soares LM, Sangueza OP, Requena L. Cutaneous myoepithelioma: an under-recognized cutaneous neoplasm composed of myoepithelial cells. Am J Surg Pathol, 2001, 25(3):348–355.
[35] Kim YC, Vandersteen DP, Chung YJ, Myong NH. Signet ring cell basal cell carcinoma: a basal cell carcinoma with myoepithelial differentiation. Am J Dermatopathol, 2001, 23(6): 525–529.
[36] Claassen SL, Royer MC, Rush WL. Granular cell basal cell carcinoma: report of a case and review of the literature. Am J Dermatopathol, 2014, 36(7):e121–e124.
[37] Barr RJ, Graham JH. Granular cell basal cell carcinoma. A distinct histopathologic entity. Arch Dermatol, 1979, 115(9): 1064–1067.
[38] Dundr P, Stork J, Povýsil C, Vosmík F. Granular cell basal cell carcinoma. Australas J Dermatol, 2004, 45(1):70–72.
[39] Kanitakis J, Chouvet B. Granular-cell basal cell carcinoma of the skin. Eur J Dermatol, 2005, 15(4):301–303.
[40] Hayden AA, Shamma HN. Ber-EP4 and MNF-116 in a previously undescribed morphologic pattern of granular basal cell carcinoma. Am J Dermatopathol, 2001, 23(6):530–532.
[41] Boscaino A, Tornillo L, Orabona P, Staibano S, Gentile R, De Rosa G. Granular cell basal cell carcinoma of the skin. Report of a case with immunocytochemical positivity for lysozyme. Tumori, 1997, 83(3):712–714.
[42] Plaza JA, Ortega PF, Bengana C, Stockman DL, Suster S. Immunolabeling pattern of podoplanin (D2-40) may distinguish basal cell carcinomas from trichoepitheliomas: clinicopathologic and immunohistochemical study of 49 cases. Am J Dermatopathol, 2010, 32(7):683–687.
[43] Ralston J, Kamino H, Liu M. Granular cell basal cell carcinoma: a diagnostically challenging case report and literature review. J Cutan Pathol, 2010, 37:A187.
[44] Chang O, Knezevich S. Granular cell basal cell carcinoma. Report of a case. J Cutan Pathol, 2012, 39:A132.
[45] Toyoda M, Morohashi M. Infundibulocystic basal cell carcinoma. Eur J Dermatol, 1998, 8(1):51–53.
[46] Fernandez-Flores A. Study of D2-40 immunoexpression of the spindle cell areas of a metaplastic basal cell carcinoma (sarcomatoid basal cell carcinoma). Appl Immunohistochem Mol Morphol, 2012, 20(5):518–522.
[47] Kyrpychova L, Carr RA, Martinek P, Vanecek T, Perret R, Chottová-Dvořáková M, Zamecnik M, Hadravsky L, Michal M, Kazakov DV. Basal cell carcinoma with matrical differentiation: clinicopathologic, immunohistochemical, and molecular biological study of 22 cases. Am J Surg Pathol, 2017, 41(6): 738–749.
[48] Kwitten J. Shadow basal cell carcinoma with acantholysis. Cutis, 2002, 69(1):57–60, 63–65.
[49] Requena L, Martín L, Fariña MC, Piqué E, Escalonilla P. Keloidal basal cell carcinoma. A new clinicopathological variant of basal cell carcinoma. Br J Dermatol, 1996, 134(5):953–957.
[50] Jones M, Bresch M, Alvarez D, Böer A. Keloidal basal cell carcinoma: not a distinctive clinicopathological entity. Br J Dermatol, 2009, 160(1):127–131.
[51] Kadono T, Okada H, Okuno T, Ohara K. Basal cell carcinoma with neuroid type nuclear palisading: a report of three cases. Br J Dermatol, 1998, 138(6):1064–1066.
[52] Yu L, Galan A, McNiff JM. Caveats in BerEP4 staining to differentiate basal and squamous cell carcinoma. J Cutan Pathol, 2009, 36(10):1074–1176.
[53] Schwob VS, Santa Cruz DJ. Palisading cutaneous fibrous histiocytoma. J Cutan Pathol, 1986, 13(6):403–407.
[54] Pinkus H. Epithelial and fibroepithelial tumors. Bull N Y Acad Med, 1965, 41(2):176–189.
[55] Reggiani C, Zalaudek I, Piana S, Longo C, Argenziano G, Lallas A, Pellacani G, Moscarella E. Fibroepithelioma of Pinkus: case reports and review of the literature. Dermatology, 2013, 226(3):207–211.
[56] Strauss RM, Edwards S, Stables GI. Pigmented fibroepithelioma of Pinkus. Br J Dermatol, 2004, 150(6):1208–1209.

[57] Sehli Attafi S, Jones M, Fazaa B, Zermani R, Rommany SR. Pinkus tumour: an unusual case. Pathologica, 2013, 105(4): 140–141.
[58] Tarallo M, Cigna E, Fino P, Lo Torto F, Corrias F, Scuderi N. Fibroepithelioma of Pinkus: variant of basal cell carcinoma or trichoblastoma? Case report. G Chir, 2011, 32(6–7):326–328.
[59] Zalaudek I, Ferrara G, Broganelli P, Moscarella E, Mordente I, Giacomel J, Argenziano G. Dermoscopy patterns of fibro-epithelioma of Pinkus. Arch Dermatol, 2006, 142(10):1318–1322.
[60] Katona TM, Ravis SM, Perkins SM, Moores WB, Billings SD. Expression of androgen receptor by fibroepithelioma of Pinkus: evidence supporting classification as a basal cell carcinoma variant? Am J Dermatopathol, 2007, 29(1):7–12.
[61] Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med, 2004, 6(6):530–539.
[62] Bazex A, Dupré A, Christol B. Génodermatose complexe de type indéterminé associant une hypotrichose, un état atrophodermique généralisé et des dégénérescences cutanées multiples (épithéliomas baso-cellulaires). Bull Soc Fr Dermatol Syphiligr, 1964, 71:206.
[63] Michaëlsson G, Olsson E, Westermark P. The Rombo syndrome: a familial disorder with vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis. Acta Derm Venereol, 1981, 61(6):497–503.
[64] van Steensel MA, Jaspers NG, Steijlen PM. A case of Rombo syndrome. Br J Dermatol, 2001, 144(6):1215–1218.
[65] Kirkham N. Tumors and cysts of the epidermis. In: Elder DE (eds). Lever's histopathology of the skin. 11th edition, Wolters Kluwer Health, Lippincott Williams & Wilkins, Philadelphia, 2015, 1006–1018.
[66] Pinkus H, Mehregan AH. A guide to dermatohistopathology. 1st edition, Appleton–Century–Croft, New York, 1969, 459.
[67] de Vries E, Trakatelli M, Kalabalikis D, Ferrandiz L, Ruiz-de-Casas A, Moreno-Ramirez D, Sotiriadis D, Ioannides D, Aquilina S, Apap C, Micallef R, Scerri L, Ulrich M, Pitkänen S, Saksela O, Altsitsiadis E, Hinrichs B, Magnoni C, Fiorentini C, Majewski S, Ranki A, Stockfleth E, Proby C; EPIDERM Group. Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study. Br J Dermatol, 2012, 167(Suppl 2):1–13.

Corresponding authors

Tiberiu Augustin Georgescu, Assistant Lecturer, MD, PhD, Department of Pathology, University Emergency Hospital, 169 Independenţei Avenue, 050098 Bucharest, Romania; Phone +40721–468622, e-mail: tiberiu.georgescu@umfcd.ro

Ana Maria Oproiu, Lecturer, MD, PhD, Department of Plastic Surgery, University Emergency Hospital, 169 Independenţei Avenue, 050098 Bucharest, Romania; Phone +40720–070 359, e-mail: anamariaoproiu@gmail.com

Received: January 20, 2018

Accepted: July 31, 2018