BASAL CELL CARCINOMA - A BRIEF REVIEW

[1]Dr. Ajay D, [2]Dr. Keerthana G, [3]Dr.Mathumala Subramanian,

[4]Dr. Vaishnavi S, [5]Dr.Sathish Kumar M

[1] CRI, [2,3]Post Graduate, [4]Senior lecturer, [5]Head of the Department

Department of Oral and Maxillofacial Pathology

Karpaga Vinayaga Institute of Dental Sciences

Chengalpattu, India

ABSTRACT :

Basal Cell Carcinoma (BCC) is the most common type of skin cancer and represents nearly 80% of all non-melanoma skin cancers worldwide. It develops from the basal cells located in the deepest layer of the epidermis, which are responsible for producing new skin cells as old ones are shed. The primary cause of BCC is prolonged exposure to ultraviolet (UV) radiation from sunlight or tanning beds, although fair skin, advancing age, genetic predisposition, and weakened immunity also increase the risk. BCC usually appears on sun-exposed areas such as the face, neck, scalp, ears, and arms. Clinically, it may present as a pearly or shiny bump, a non-healing ulcer, a reddish patch, or a scar-like lesion. Although the tumor grows slowly and rarely spreads to distant organs, it can progressively invade nearby tissues if left untreated. Advanced lesions may destroy skin, cartilage, nerves, and even underlying bone, causing significant deformity and functional impairment. Early diagnosis is important because treatment at an initial stage provides excellent outcomes and minimal scarring. Diagnosis is confirmed through clinical examination and biopsy. Common treatment options include surgical excision, Mohs micrographic surgery, cryotherapy, curettage, electrodessication, radiation therapy, and topical medications in selected cases. Preventive measures such as regular sunscreen use, protective clothing, avoiding excessive sun exposure, and periodic skin examinations can greatly reduce the risk of developing BCC and help detect lesions early.

KEYWORDS :

Slow-growing,Locally invasive ,Rarely metastasizes, Local destruction, Uv radiation.

INTRODUCTION :

Basal Cell Carcinoma (BCC) is the most common malignant tumor of the skin, contributing to approximately 80–90% of all skin cancer cases worldwide[1,2]. It originates from the basal cells present in the deepest layer of the epidermis and from skin appendages such as hair follicles. Chronic exposure to ultraviolet (UV) radiation, especially from sunlight, is considered the major causative factor, while fair skin, increasing age, genetic predisposition, and immunosuppression further increase susceptibility. BCC commonly affects sun-exposed regions including the face, scalp, neck, and ears. Clinically, it may appear as a pearly papule, nodular lesion, ulcer, or non-healing sore with rolled borders. Although the tumor rarely metastasizes to distant organs, it is locally invasive and can progressively infiltrate surrounding tissues if untreated. Advanced lesions may destroy adjacent skin, cartilage, muscle, and bone, leading to cosmetic deformity and functional impairment. Recurrence is relatively common, particularly when lesions are inadequately treated or located in high-risk facial areas. Early diagnosis through clinical examination and biopsy is therefore essential to prevent complications and improve treatment outcomes. Management

options include surgical excision, Mohs micrographic surgery, cryotherapy, radiation therapy, and topical chemotherapeutic agents depending on the size, location, and subtype of the lesion.[3,4]

EPIDEMIOLOGY:

Most common cancer globally, especially in fair-skinned populations Common in **elderly (6th–8th decade)** with slight male predominance [5,6] Increasing incidence due to **UV exposure and aging population** [7,8] About **70% occur on face**, especially nose and eyelids

ETIOLOGY AND RISK FACTORS :

BCC develops due to a combination of **genetic, environmental, and immunological factors**:

- Major risk factors ; **Ultraviolet (UV) radiation (most important)** ,Fair skin (Fitzpatrick type I & II),Childhood sun exposure,Ionizing radiation,Immunosuppression (HIV, transplant patients),Exposure to carcinogens (e.g., arsenic),Genetic syndromes:
    - Xeroderma pigmentosum
    - Gorlin syndrome

- Additional risk factors ; Chronic scars, burns, trauma, and inflammation ,Post-vaccination scars (rare but reported) [9,10]

PATHOGENESIS :

The key molecular mechanism involves **abnormal activation of the Hedgehog (HH) signaling pathway**:

Normally, this pathway regulates embryonic development, cell differentiation, and tissue repair. In healthy cells, the PTCH1 receptor suppresses the activity of another protein called Smoothened (SMO). When the Hedgehog ligand binds to PTCH1, this inhibition is removed, allowing controlled cell growth. In BCC, mutations in the PTCH1 gene are the most common abnormality, leading to continuous activation of SMO even in the absence of signaling molecules. Mutations in the SMO gene itself can also independently activate the pathway. In addition, mutations in the TP53 tumor suppressor gene impair DNA repair and apoptosis, allowing damaged cells to survive and proliferate. Persistent activation of the HH pathway ultimately causes uncontrolled cellular proliferation, tumor formation, and prolonged survival of malignant basal cells. This pathway forms the basis for targeted therapies such as Hedgehog pathway inhibitors used in advanced BCC treatment.

Increased Cell Proliferation, Tumor Growth, and Survival

Abnormal molecular signaling in BCC results in excessive proliferation of basal cells and resistance to normal growth regulation. Continuous activation of oncogenic pathways stimulates the production of proteins that promote cell cycle progression and inhibit programmed cell death (apoptosis). As a result, mutated basal cells multiply rapidly and accumulate within the epidermis and surrounding tissues. These tumor cells also develop survival advantages that allow them to persist despite cellular stress or immune responses. The increased proliferative activity contributes to the slow but locally invasive growth pattern characteristic of BCC. Over time, the tumor can invade adjacent skin, connective tissue, cartilage, and even bone if left untreated. Enhanced tumor survival mechanisms also explain the tendency of some lesions to recur after incomplete treatment.

PI3K/AKT Pathway

The PI3K/AKT signaling pathway plays an important supportive role in the pathogenesis of Basal Cell Carcinoma by promoting cell survival, proliferation, and metabolic activity. Activation of phosphoinositide 3-kinase (PI3K) leads to stimulation of AKT, a protein kinase involved in regulating cell growth and preventing apoptosis. In BCC, this pathway may become overactive due to molecular cross-talk with the Hedgehog pathway or other oncogenic signals. Increased AKT activity enhances tumor cell survival and allows malignant cells to resist normal regulatory mechanisms. The pathway also contributes to angiogenesis and nutrient utilization, helping tumor cells sustain their growth. Because of its role in promoting malignancy, the PI3K/AKT pathway is considered a potential therapeutic target in aggressive or treatment-resistant BCC cases.

EGFR Pathway

The Epidermal Growth Factor Receptor (EGFR) pathway is another molecular mechanism involved in the progression of Basal Cell Carcinoma. EGFR is a transmembrane receptor that regulates cellular growth, differentiation, and repair processes. When activated excessively, EGFR stimulates downstream signaling cascades such as RAS/MAPK and PI3K/AKT, leading to uncontrolled proliferation of keratinocytes and tumor cells. In BCC, overexpression or abnormal activation of EGFR may enhance tumor aggressiveness and invasive behavior. EGFR signaling also promotes cellular migration and tissue invasion, contributing to local destruction caused by advanced lesions. Research suggests that interaction between EGFR and Hedgehog signaling pathways may further accelerate carcinogenesis. Therefore, EGFR-targeted therapies are being investigated as potential adjunctive treatments in certain skin cancers.

Hippo-YAP Pathway

The Hippo-YAP signaling pathway is an important regulator of organ size, tissue regeneration, and cell proliferation. Under normal conditions, the Hippo pathway suppresses excessive cell growth by inhibiting the activity of YAP (Yes-associated protein), a transcriptional co-activator. In Basal Cell Carcinoma, dysregulation of this pathway results in increased YAP activation, which stimulates genes involved in proliferation, survival, and stem cell maintenance. Enhanced YAP activity promotes uncontrolled growth of basal cells and contributes to tumor progression. The Hippo-YAP pathway may also interact with Hedgehog signaling, further intensifying oncogenic activity within the tumor microenvironment. Studies indicate that abnormal YAP signaling is associated with increased invasiveness and recurrence of BCC, making it a promising target for future molecular therapies.

Immune Evasion in Basal Cell Carcinoma:

Immune evasion is a crucial factor that allows Basal Cell Carcinoma cells to survive and progress despite the body's defense mechanisms. Tumor cells modify the local immune environment by producing immunosuppressive cytokines and altering immune cell activity. This creates a microenvironment that reduces effective anti-tumor immune responses and enables continued tumor growth. BCC cells can suppress T-cell activation, reduce antigen presentation, and inhibit inflammatory responses that would normally destroy abnormal cells. Chronic ultraviolet (UV) radiation exposure further weakens local immune surveillance and contributes to carcinogenesis. The ability of BCC to evade immune destruction explains its persistence and recurrence in some patients and has led to interest in immunotherapy as a treatment approach.

IL-6 and IL-10 Cytokines

Interleukin-6 (IL-6) and Interleukin-10 (IL-10) are important cytokines involved in the immune evasion mechanisms of Basal Cell Carcinoma. IL-6 is a pro-inflammatory cytokine that promotes tumor growth, angiogenesis, and survival of malignant cells. Elevated IL-6 levels stimulate signaling pathways that enhance proliferation and resistance to apoptosis. IL-10, on the other hand, is an immunosuppressive cytokine that inhibits T-cell activation and reduces the effectiveness of anti-tumor immune responses. Increased production of IL-10 within the tumor microenvironment helps BCC cells escape immune surveillance and persist for prolonged periods. Together, these cytokines create a balance that favors tumor progression while suppressing protective immune activity.

TGF-β (Transforming Growth Factor-Beta)

Transforming Growth Factor-Beta (TGF-β) is a multifunctional cytokine that plays a dual role in cancer development. In the early stages of tumor formation, TGF-β may suppress cell proliferation and act as a tumor inhibitor. However, in established Basal Cell Carcinoma, it often promotes tumor progression by enhancing immune suppression, tissue invasion, and fibrosis. TGF-β inhibits the activity of cytotoxic T lymphocytes and natural killer cells, allowing tumor cells to evade immune destruction. It also stimulates extracellular matrix remodeling and epithelial-mesenchymal transition, which contribute to local invasiveness. Increased TGF-β signaling within the tumor microenvironment supports tumor survival and chronic progression. Due to its significant role in carcinogenesis and immune modulation, TGF-β is considered an important target for future cancer therapies.

CLINICAL FEATURES :

BCC may present with a lesion which has enlarged with time, is non-healing and which may bleed or ulcerate; these aspects may also be accompanied by pruritus. The classical clinical description of such a tumor is that of a shiny, pearly, smooth papule/nodule with conspicuous, dilated and arborizing blood vessels, often with erosions or ulcerations and rolled margins. The clinical aspects vary with the histological type of the tumor (discussed below);thus, the classical clinical description may correspond to the nodular type of BCC, while the discovery of a circumscribed,annular, thin patch or plaque with/without scales, central clearing and rolled borders can be observed in superficial BCC; scar-like lesions or poorly defined, infiltrative, shiny plaques (which can be flat or depressed) can indicate the presence of an infiltrative or morphoeic/sclerosing BCC, and the pigmented variant of BCC can be clinically confused with melanoma or Spitz-Reed nevus.The fibroepithelial variant of BCC is frequently mistaken for an acrochordon or a seborrheic keratosis, presenting as sessile plaque or pedunculated papule or nodule, which can be flesh-colored or erythematous. Infundibulocystic BCCs present as pearly papules that are well circumscribed, being frequently mistaken for benign follicular processes [11,12]

HISTOPATHOLOGY :

The histopathology of BCC is largely characterized by aggregates of basal cells with a small cytoplasm and large, hyperchromatic nuclei, apoptotic cells, all included in a fibro- myxoid stroma, with tumor retraction spaces. Angiogenesis is an indicator of tumor development and its progression [13,14]

Nodular BCC

Nodular BCC presents microscopically as large nests or islands of malignant basaloid cells with central, haphazard cell arrangement and peripheral palisading, tumor-stroma clefting,
mucoid/myxoid stroma with spindle cells, with/without amyloid deposits; sometimes the tumor stroma has a collagenous, keloidal-type aspect.

Superficial BCC

Superficial BCC develops as small islands or lobules of malignant basaloid cells with peripheral palisading, localized in the superficial dermis, with a connection to the epidermis and within a myxoid stroma, associated with a lichenoid, band-like, inflammatory infiltrate.

Morpheaform BCC

Sclerosing Bcc strands/chords of tumor cells (with a thickness of 1-5 cells, and also with angulated ends) found in a collagenous type of stroma, with seldom tumor-stroma clefting. It infiltrates deeply and differs from the infiltrating subtype of BCC by the stromal characteristics, the latter lacking the highly collagenous stroma.

Infiltrating BCC

Infiltrating BCC is a subtype composed mainly of chords or thin nests of tumor cells (with a thickness of >5-8 cells) which infiltrate deeply, with angulated edges and have an
irregular, permeating invasion pattern at the tumor edge. It frequently overlaps with morphoeic/sclerosing BCC and can be found with a nodular component.

Pigmented BCC

Pigmented BCC is a variant of nodular or superficial BCC, which contains melanin pigment derived from an increased number of dendritic melanocytes within the malignant tumor
nests, being found within the malignant basaloid cells or the macrophages which surround the malignant proliferation.

TREATMENT:

The surgical treatment of BCC is the main approach through which the entire tumor mass can be excised, and the cosmetic and functional aspects can be preserved, providing optimal
results for the patient. The surgical excision needs to be made with at least 4-mm margins in low-risk BCC, whereas for high-risk ones, margins of at least 6 mm should be ensured.[15,16]

Curettage or electrodessication are older techniques, recommended in superficial BCC or low-risk tumors, having the downside of not allowing a histopathological examination of surgical margins. [17] Cryosurgery uses freeze-thaw cycles in order to destroy the malignant tumor cells, and, as with curettage and electrodessication, does not allow the microscopic examination of tumor margins and is mostly recommended in low-risk cases, such as superficial BCC[18,19] Laser therapy, such as super pulsed carbon dioxide laser therapy or pulsed neodymium-based laser therapy, can be used alone or in combination with other therapeutic approaches. It has proven to have small recurrence rates of up to 1.8% in
5 years, although it presents with local adverse effects, such as soreness, edema, hyperemia and scarring.[20,21]

CONCLUSION:

Basal Cell Carcinoma is a **common yet largely preventable and treatable skin cancer**. While it rarely metastasizes, its **local invasiveness and recurrence potential** require prompt diagnosis and appropriate management. Emerging insights into **genetic pathways and immune mechanisms** have improved targeted therapies, enhancing patient outcomes.

REFERENCES :

1. Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, Nehal KS and Rossi AM: Basal cell carcinoma: Epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. J Am Acad Dermatol 80: 303-317, 2019.
2. Matsui Y, Makino T, Takemoto K, Kagoyama K and Shimizu T: Co-existence of basal cell carcinoma and squamous cell carcinoma in a single burn scar region. Burns Open 4: 64-66, 2020.
3. Lai K, Chan E and Ko SC: Combination of squamous cell carcinoma and basal cell carcinoma arising from a giant verruca vulgaris involving the eyelid. Am J Ophthalmol Case Rep 21:100858, 2020
4. Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Australas J Dermatol. 2015;56:258–67. https://doi.org/10.1111/ajd.12282.
5. Walker H, Maitland C, Tabbakh T, Preston P,Wakefield M, Sinclair C. Forty years of Slip! Slop!Slap! A call to action on skin cancer prevention for Australia. Public Health Res Pract. 2022;32(1):1–7.
6. Christenson LJ. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA. 2005;294:681.
7. McDaniel, B.; Bermudez, R. Epitheliomas, Basal Cell; StatPearls: Boston, MA, USA, 2018; Volume 2.
Jiang, J. Hedgehog Signaling Mechanism and Role in Cancer. Semin. Cancer Biol. 2022, 85, 107–122. [CrossRef]
8.Bakshi, A.; Chaudhary, S.C.; Rana, M.; Elmets, C.A.; Athar, M. Basal Cell Carcinoma Pathogenesis and Therapy Involving
Hedgehog Signaling and Beyond. Mol. Carcinog. 2017, 56, 2543–2557. [CrossRef]
9.. Dika, E.; Scarfì, F.; Ferracin, M.; Broseghini, E.; Marcelli, E.; Bortolani, B.; Campione, E.; Riefolo, M.; Ricci, C.; Lambertini, M. Basal
Cell Carcinoma: A Comprehensive Review. Int. J. Mol. Sci. 2020, 21, 5572. [CrossRef]
10. Evans, D.G.; Oudit, D.; Smith, M.J.; Rutkowski, D.; Allan, E.; Newman, W.G.; Lear, J.T. First Evidence of Genotype-Phenotype
Correlations in Gorlin Syndrome. J. Med. Genet. 2017, 54, 530–536
11. Evans, D.G.; Oudit, D.; Smith, M.J.; Rutkowski, D.; Allan, E.; Newman, W.G.; Lear, J.T. First Evidence of Genotype-Phenotype
Correlations in Gorlin Syndrome. J. Med. Genet. 2017, 54, 530–536. [CrossRef]
12. Pietrobono, S.; Gagliardi, S.; Stecca, B. Non-Canonical Hedgehog Signaling Pathway in Cancer: Activation of GLI Transcription
Factors beyond Smoothened. Front. Genet. 2019, 10, 556. [CrossRef] [PubMed]
13. Pellegrini, C.; Maturo, M.G.; Di Nardo, L.; Ciciarelli, V.; Gutiérrez García-Rodrigo, C.; Fargnoli, M.C. Understanding the Molecular
Genetics of Basal Cell Carcinoma. Int. J. Mol. Sci. 2017, 18, 2485. [CrossRef] [PubMed]
14. Abe, Y.; Oda-Sato, E.; Tobiume, K.; Kawauchi, K.; Taya, Y.; Okamoto, K.; Oren, M.; Tanaka, N. Hedgehog Signaling Overrides
P53-Mediated Tumor Suppression by Activating Mdm2. Proc. Natl. Acad. Sci. USA 2008, 105, 4838–4843. [CrossRef] [PubMed]

15. Wei, L.; Xu, Z. Cross-Signaling among Phosphinositide-3 Kinase, Mitogenactivated Protein Kinase and Sonic Hedgehog Pathways
Exists in Esophageal Cancer. Int. J. Cancer 2011, 129, 275–284. [CrossRef] [PubMed]
16. Kaporis, H.G.; Guttman-Yassky, E.; Lowes, M.A.; Haider, A.S.; Fuentes-Duculan, J.; Darabi, K.; Whynot-Ertelt, J.; Khatcherian,
A.; Cardinale, I.; Novitskaya, I.; et al. Human Basal Cell Carcinoma Is Associated with Foxp3+ T Cells in a Th2 Dominant
Microenvironment. J. Investig. Dermatol. 2007, 127, 2391–2398. [CrossRef] [PubMed]
17. Tjiu, J.W.; Chen, J.S.; Shun, C.T.; Lin, S.J.; Liao, Y.H.; Chu, C.Y.; Tsai, T.F.; Chiu, H.C.; Dai, Y.S.; Inoue, H.; et al. Tumor-Associated
Macrophage-Induced Invasion and Angiogenesis of Human Basal Cell Carcinoma Cells by Cyclooxygenase-2 Induction. J. Investig.
Dermatol. 2009, 129, 1016–1025. [CrossRef] [PubMed]
18. Westin, A.T.; Gardinassi, L.G.; Soares, E.G.; Da Silva, J.S.; Donadi, E.A.; Da Silva Souza, C. HLA-G, Cytokines, and Cytokine
Receptors in the Non-Aggressive Basal Cell Carcinoma Microenvironment. Arch. Dermatol. Res. 2022, 314, 247–256. [CrossRef]
[PubMed]
19. Jee, S.H.; Shen, S.C.; Chiu, H.C.; Tsai, W.L.; Kuo, M.L. Overexpression of Interleukin-6 in Human Basal Cell Carcinoma Cell Lines
Increases Anti-Apoptotic Activity and Tumorigenic Potency. Oncogene 2001, 20, 198–208. [CrossRef] [PubMed]
20. Chiang, E.; Stafford, H.; Buell, J.; Ramesh, U.; Amit, M.; Nagarajan, P.; Migden, M.; Yaniv, D. Review of the Tumor Microenviron-
ment in Basal and Squamous Cell Carcinoma. Cancers 2023, 15, 2453. [CrossRef]
21. Lesiak, A.; Czuwara, J.; Kami´nska-Winciorek, G.; Kiprian, D.; Maj, J.; Owczarek, W.; Placek, W.; Rudnicka, L.; Rutkowski, P.;
Sobjanek, M.; et al. Basal Cell Carcinoma. Diagnostic and Therapeutic Recommendations of the Polish Dermatological Society.
Przegl. Dermatol. 2019, 106, 107–126. [CrossRef]