Basal Cell Carcinoma: A Review

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Abstract*— The present article reviewed that basal cell carcinoma (BCC) is a malignant skin tumor with slow growth and limited invasion that primarily affects people with fair skin, most of whom are Caucasian. This kind of skin cancer is the most prevalent kind. BCC is renowned for its locally invasive characteristics and slow growth. It frequently forms a three-dimensional infiltration of surrounding tissue, resulting in uneven finger-like extensions that stay connected to the primary tumor mass. Despite having a low death rate, basal cell carcinoma can cause significant morbidity because of its propensity for invasive development and localized tissue damage. The prevalence of basal cell carcinoma (BCC) decreases dramatically after the age of forty, but a worrying trend is indicated by the growth in BCC incidence among the youngest population, especially in women. This increase is likely due to increased exposure to UV radiation from the sun and artificial sources. Basal keratinocytes, which are cells found in the basal layer of the epidermis as well as in hair follicles and eccrine sweat ducts, are the source of basal cell carcinoma (BCC). Histologically, BCC cells frequently have big nuclei and show signs of basophilic staining, which makes them seem blue under a microscope. BCC patients have a variety of treatment choices, such as topical medicines in some circumstances or surgical methods to remove the tumor. Prevention is key, with special attention to sun protection techniques like wearing protective clothes, using sunscreen, and limiting one's exposure to the sun. Frequent skin examinations are crucial for early identification, enabling more efficient treatment, and lowering the risk of side effects related to untreated BCC. It is advisable to seek quick medical examination for proper care and timely intervention if any worrisome changes in the skin are identified.

I. INTRODUCTION

Basal cell carcinoma is indeed a common type of skin cancer, and it was first described by Jacob in 1827.While it is a prevalent skin cancer, it's important to note that it is not that it is most common malignant neoplasm in humans overall.[1]

Basal cell carcinoma (BCC) is indeed a slow-growing, locally invasive malignant skin tumor that predominantly affects individuals with fair skin, often Caucasian descent. It is the most common type of skin cancer. BCC is known for its slow growth and locally invasive nature. It often infiltrates surrounding tissue in a three-dimensional fashion, forming irregular finger-like projections that remain contiguous with the main tumor mass. This unique growth pattern underscores the importance of early detection and treatment to prevent further invasion and potential complications. Regular skin examinations and consulting a dermatologist are key in managing BCC.[1] Metastatic basal cell carcinoma is indeed rare, and it typically arises from primary tumor that is neglected, large, ulcerated, locally invasive, and destructive, despite repeated attempts at surgical removal or radiotherapy. This behavior is unusual for basal cell carcinoma, which is generally slow-growing and non-metastatic.[2]

Basal cell carcinoma is often associated with low mortality rates, but it can lead to notable morbidity due to it's potential for local tissue destruction and invasive growth. BCC incidence significantly after the age of 40 years, but the rise in basal cell carcinoma incidence among the youngest population, particularly in womens, suggests a concerning trend likely linked to increased exposure to UV radiation from the sun and artificial souces. Certain genodermatoses, such as Gorlin syndrome (nevoid basal cell carcinoma syndrome), can increase the predispositon to developing basal cell carcinomas at an earlier age.[15]

Indeed, basal cell carcinoma often exhibit distructive characteristics in their early stages, appearing translucent or pearly with raised areas where dilated vessels may be visible. As they progress, the diverse patterns include nodulo-ulcerative (rodent ulcer), morphoeic, superfical, pigmented and keloid variants

can make the classification challenging. Differntiating these variants is crucial for determinig the most appropriate treatment apporach.[14]Basal cell carcinoma can leads to significant damage and disfigurement of local tissues if proper treatment is not administered promptly or if there is a delay in seeking medical attention. Early diagnosis and appropriate medical intervention are essential in managing BCC to minimize potential complications.[16]

Tamoxifen induction in K14-CREER/RosaSmoM2 resulted in positive cell expression in various epidermal regions , allowing the tracking of independent clones until BCC development. This apporach aimed to pinpoint the specific cells contributing to BCC formation in different epidermal compartments.[30]

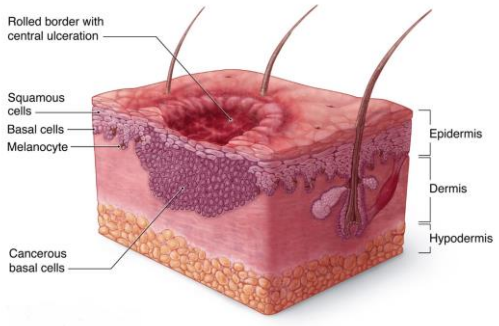

Fig.1: Development of basal cell carcinoma

1. Pathophysiology of BCC:

Basal cell carcinoma (BCC) originates from basal keratinocytes , which are cells located in the basal layer of the epidermis, asa well as in hair follicles and eccrine sweat ducts. Histologically, BCC cells typically exhibit basophilic staining, appearing blue under microscopic examination, and they often have a large nuclei.[17]

One key characteristic of BCC is its limited potential for metastasis. Unlike more aggressive forms of skin cancer, BCC tends to grow locally and is generally incapable of spreading through the bloodstream(metastasizing via blood) or the lymphatic system. This is largely attributed to its growth pattern and dependence on surrounding stroma, the connective tissue that provides structural support.[17]

BCC tends to invade and locally destroy surrounding tissues rather than spreading to distant organs. This characteristic makes BCC a relatively slow-growing and less invasive type of skin cancer compared to other skin malignancies. While BCC can cause significant local damage if left untreated, its low metastatic potential is a favorable aspect in terms of overall prognosis and treatment options. Regular monitoring and early intervention are crucial for managing BCC effectively.[17]

2. Etiology and pathogenesis of basal cell carcinoma:

Basal cell carcinoma (BCC) development is strongly linked to sun exposure. Factors such as fair skin, poor tanning ability, blond hair, blue eyes, increased age, male sex, and significant lifetime sun exposure are all associated with an increased risk of developing BCC. Protecting your skin from sun rays is crucial in reducing the risk of BCC and other skin cancer.[3]

- UV radiation: UV radiation plays a dual role in the development of BCC. It causes DNA damage in skin cells, which can lead to mutations and uncontrolled cell growth, contributing to cancer development. Additionally, UV radiation can suppress the immune system's ability to recognize and eliminate cancerous cells, making it easier for skin cancers like BCC to form and progress. Protecting your skin from excessive UV exposure is essential for reducing the risk of BCC and other skin cancer.[4]

  The study findings suggest a correlation between an increased risk of basal cell carcinoma and certain sun exposure patterns during childhood or adolescence. Subjects with a light tan after repeated sun exposure had a higher frequency of BCC diagnosis(OR=3.14), and there was an elevated risk (OR=4.53) associated with individuals who usually experienced painful burns with blisters after prolonged sunlight exposure during that period.[20]

  Indeed, the relationship between the risk of BCC and factors such as the amount , timing, and pattern of exposure to UV radiation is complex and not fully understood. Reseach continues to gain a more comprehensive understanding of the mechanisms and contributing factors.[23]
- Ionizing radiation: The linked between prolonged exposure to low-dose ionizing radiation and an increased risk of subsequent nonmelanoma skin cancer(NMSC), specifically basal cell carcinoma(BCC), suggests a potential correlation

between radiation exposure and skin cancer development . This association has been observed in individuals who have undergone extended periods of ionizing radiation treatment.[5]

Additional risk of BCC associated with ionizing radiation treatment for specific medical conditions such as goiters, ankylosing spondylitis, acute lymphocytic leukemia , and astrocytoma. In the context of these medical treatments, ionizing radiation is employed, and the increased risk for BCC could be attributed to the impact of radiation on skin cells during therapeutic interventions.[5]

The mechanism underlying this association likely involves the ability of ionizing radiation to induce DNA damage. Prolonged or repeated exposure to low dose ionizing radiation can lead to cumulative genetic alterations in skin cells, potentially increasing the susceptibility to the development of skin cancers, including basal cell carcinoma.[5]

- Chemical carcinogens: Chemical carcinogens like arsenic, tar, psoralen, and pesticidesare associated with an increased risk of nonmelanoma skin cancer, particularly squamous cell carcinoma (SCC). Furthermore, the exposure to psoralen combined with UVA radiation in PUVA therapy for psoriasis has been linked to an elevated risk of both basal cell carcinoma (BCC) and SCC in some studies. However, it's noteworthy that conflicting finding exist, with certain studies suggesting no heightened risk of BCC in patients undergoing PUVA therapy. The nuances in research highlight the complexity of assessing the risks and benefits associated with specific treatments for skin conditions.[4]

  The study reveals that occupational exposure to various chemicals, both organic and non-organic solvents, and organophosphate compounds is identified as a risk factor for basal cell carcinoma. This suggest that individuals with certain occupational backgrounds, involving a contact with this substance, face an increased likehood of developing a basal cell carcinoma, a common form of skin cancer.[4]

  In addition to occupational exposures, the study underscores the risk associated with using tar for cosmetic purposes. The use of tar in cosmetic product appears to contribute to an elevated risk of basal cell carcinoma, emphasizing the importance of considering not only occupational settings but also personal cosmetic practices in assessing skin cancer risk.[22]

  This information is crucial for occupational safety protocols and may guide individuals in making informed choice about occupational environments and cosmetic products to mitigate the risk of developing basal cell carcinoma.[22]

- Genetic: Xeroderma pigmentosum (XP) is indeed characterized by severe photosensitivity due to defects in DNA repair mechanisms,making patients prone to cutaneous cancers like squamous cell carcinoma (SCC), basal cell carcinoma(BCC), and malignant melanoma.

  Rothmund-Thomson syndrome,on the other hand , is associated wit mutations in DNA helicase genes and has been linked ta an increased risk of developing basal cell carcinoma (BCC) specifically.[6]

  Both condition highlight the importance od DNA repair mechanisms in preventing the development of skin cancers.Regular monitoring and sun protection are crucial for individuals with these conditions to reduce their risk of skin cancer.[6]

  In sporadic basal cell carcinoma , there's an observed association where DNA repair capacity below the upper 30thpercentile is linked to a 2-3 fold incease in BCC relative risk. However, it's worth noting that some studies have reported increased repair in BCC patients. Factors such as batch variability, age, family history of skin cancer, and current sun exposure may introduce confounding variables that can impact and complicate study result.[21]

- Viruses: Several authors demonstrated association between infection by oncogenic types of human papillomavirus (HPV) and the development of basal cell carcinoma suggests that specific HPV strains, known for their cancer causing potential, may be implicated in the initiation or progression of BCC.[6]

  The research conducted by Harwood and Proby, contributes to this understanding by showing that HPV has a capacity to interfere with UV-induced apoptosois. Apoptosis is a programmed cell death process crucial for eliminating damaged or potentially cancerous cells. By disrupting UV-induced apoptosis, HPV may disrupt the normal cellular response to ultraviolet radiation , allowing

cells to survive that would typically undergo programmed cell death.[6]

In essence, these findings propose a potential mechanistic link between HPV infection, the inhibition of apoptosis triggered by UV radiation , and the development of basal cell carcinoma. This research enhances our understanding of how viral infections particularly by oncogenic HPV types, may impact cellular processes and contribute to the development of certain cancers, such as BCC.[6]

- Diet risk: There are various consideration in understanding the relationship between nutrient intake and the risk of basal cell carcinoma of the skin. One key point is that the timinig of dietary assessment might not align with the critical period for nutrient effects in the process of cacinogenesis. Additionally, cumulative lifetime sun exposure is highlighted as a significant risk factor for BCC.[24]

  The idea that diet during childhood or young adulthood could modify the impact of sun exposure, and that assessing diet in middle adulthood might miss this interaction, emphasizes the importance of considering long term influences on cancer risk.

  The swift risk reduction observed with isoretinoin administration implies a potential role in the late-stage promotion of BCC, indicating that interventions at specific stages could have varying effects.[24]

  The acknowledgment of possible biologic interactions between dietary factors and carcinogenic events in epithelial cancer causation adds a layer of complexity. However, the statement also recognizes the dominance of ultraviolet radiation's strong effect, which might overshadow any potential contributions from nutrient effects on BCC.[24]

  Despite leaving open the possibility that large supplemental doses of certain nutrients could reduce risk, the study did not find a decrease in BCC risk among women consuming supplemental vitamins A,C,E or D. This underscores the challenges in estabilishing a clear association between nutrient intake and BCC risk, given the multifaceted nature of the factors involved.[24]

- Stages of BCC

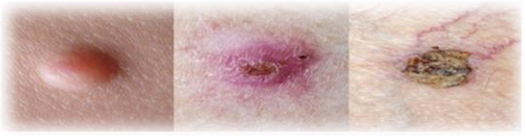

Fig.:2 Stages of basal cell carinoma

IV. EPIDEMOLOGY

Basal cell carcinoma (BCC) is most common skin cancer , perticullary among fare skinned adults.Australia has one of the highest incidence of skin cancer globally (up to 1000/100,000) inhabitant per year , followed by the USA (212-407/100,000) female and male inhabitants respectively per year and Europe (mean range from 76.21/100,000) person years in the UK to 157 /100,000 person-years in 2009 in Netherlands.[7] It's concerning that there were around 115,000 new cases of non-melanoma skin cancer in Brazil in 2010, accounting for approximately 2.2% of dermatologic vists.[18] The cancer statistics from 2014 indicate that the average age at the first diagnosis of basal cell carcinoma patients in Germany was 72 years, and 52% of these patients were male. Regular screening and awareness are essential for early detection and treatment.[19]

It's notable that the population-based study in Rochester, Minnesota, found an age-standardized annual incidence for basal cell carcinoma of 146 cases per 100,000 persons in Caucasian men and women. In contrast, the study in Kauai, Hawaii, reported a combined incidence of 422 cases per 100,000 peoples among Caucasian reside nts, marking the highest documented incidence in the U.S. at the time of publication in 1993. These figures highlight regional variations in basal cell carcinoma incidence.[10]

Basal cell carcinoma is indeed most commonly diagnosed in individuals over 50 years old,with female/male ratio of 2:1. However, some patient develop BCC at an earlier age(<40 years). An individuals with genetic predisposition syndromes like xeroderma pigmentosum or basal cell nevus syndrome have an increased risk of developing basal cell carcinoma at an earlier age, often before 20 years old. BCC is considered one of the most highly mutated

human tumor (65 mutations/megabase).[7]It's plausible that changes in the ratio of BCC to squamous cell carcinoma(SCC) in the USA from 4:1 to 1:1 in 2012 could be influenced by earlier non-surgical treatment of SCC lesions.[8,9]

Immunosuppression is a significant risk factor for the development of basal cell carcinoma. Individuals who undergo organ transplantation, particularly kidnet transplant recipents, often require immunosppressive medications to prevent rejection of the transplanted organ. However, these medications can weaken the immune system's ability to detect and eliminate abnormal cells, increasing the risk of skin cancers, including BCC. The risk is notably higher, with more than a 10 fold increase in BCC incidence among immunosuppressed individuals. Regular skin checks and sun protection are crucial for those with a history of immunosuppression.[7]

V. HISTOPATHOLOGY

Basal cell carcinoma classified on the based of histopathological features; the indolent-growth subtypes include nodular and superficial, align with clinical nodular and superficial subtypes(fig.3i). On the other hand the aggressive-growth subtype consist of morpheaform, infiltrative,micronodular, and basosquamous often association with higher recurrence rates and extensive local distruction.

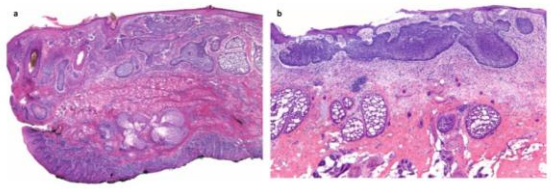

Fig.3:i. Indolent growth

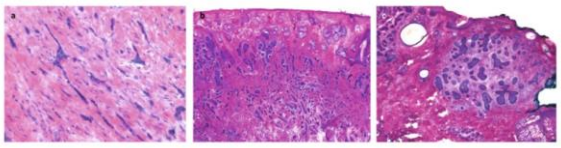

Fig.3:ii.Aggresive-growth

These histopathologic patterns can coexist in single specimen, forming what's known as a mixed histology tumor. The prevalence of this phenomenon,accounting for around 40 percent of primary BCCs, highlights the complexity of tumor compositions in histopathology.[10]

VI. INDOLENT-GROWTH HISTOLOGIC SUBTYPES

- Nodular basal cell carcinoma:-

It imphasizing the presence of dark-blue-staining basaloid keratinocytes with peripheral palisading and clefting throughout the dermis.[10]

The features of nodular basal cell carcinoma, emphasizing its potential extension patterns, clinical presentations such as flat enduring plaques from endophytic nodules, and the varied appearances, including hemorrhagic lesions that may resemble hemangioma or pigmented melanoma. The designation of larger lesions with central necrosis as ulcusrodens and the histological revelation of nest-like infiltration from basaloid cells.[26]

- Superficial basal cell carcinoma:-

It involves basaloid cells proliferating parallel to the epidermal surface, typically not extending beyond the papillary dermis.

Superficial basal cell carcinoma ranks as the second most prevalent clinical subtype, contributing up to 15 percent of cases. Characterized by well defined, scaly, pink to red lesions-macules, patches, thin papules, or plaques it may exhibit a crust or a thin rolled border with fine translucent small papules. Spontaneous regression can result in atropic, hypopigmented areas, and variable melanin pigment mat be present. Notably, superficial BCCs tend to occur on the trunk and extremities, distinguishing them from other subtypes that commonly affect the head and neck.[10]

Aggerasivegrowth histologicsubtypes:-

- Morpheaformbesal cell carcinoma:-

The high-power view reveals small irregulartongues collagenized stroma. This characteristic pattern is typical of morpheaformsubtype.[10]

The morpheaform variant of basal cell carcinoma is the least common type. Clinically, it presents as a firm, flat to slightly raised lesion with a pale-white to yellow

appearance, resembling scar tissue. Typically found on the face, especially around the nose, forehead, or cheeks, it has a waxy texture, tends to be recurrent, has ill-defined borders, lacks ulceration, and exhibits local aggressiveness. Eradicating this type is particularly challenging.[29]

- Infiltrative basal cell carcinoma:-

In infiltrative basal cell carcinoma a low-power view often reveals basaloid aggregates with divers size and shape.Notably,these aggregate tends to decrease in size as you move from the superficial to the deep portion of the neoplasm,reflecting the invasive nature of the carcinoma.[10]

Histological variants exhibit an infiltrative growth pattern, characterized by long, thin strands of tumour cells penetrating deeply among collagen fascicles. Superficial layers often show a soild growth pattern, while the infiltrative type in typically found in lower or peripheral tumor layers. Incomplete excision may categorize the tumour as nodular initially, with the infiltrative type revealed during re-excision.[27]

- Micronodular basal cell carcinoma:-

Micronodular basal cell carcinoma presents as a plaque-like structure, with a heightened risk of recurrence. Pathologically akin to nodular basal cell carcinoma, it features smaller micronodules of basaloid cells, about the sizeof hair bulbs, and exhibits minimal palisading. The surroung stroma takes on a myxoid quality.[28]

In typically presents as small, nodular ,irregular aggregates of basaloid neoplastic cells. These clusters are often surrounded by a cellular myxoid stroma,contributing to the characteristic microscopic appearance of this subtype of basal cell carcinoma.[10]

- Diagnosis:

Basal cell carcinoma present diagnostic challenges due to their resembalance to the various skin conditions. Clinically, differentiating BCC from squamous cell carcinoma, keratocanthoma, actinic keratosis, or molluscum contagiosum can be difficult. Flesh-colored intradermal nevi may be indistinguishable from BCC, and pigmented BCCs can mimic seborrheic keratosis, nevi, angiokeratoma, or even malignant melanoma. Scelerosing BCC, resembling a scale, might be easily overlooked. Superficial BCC is sometimes mistaken for psoriasis or nummular eczema, yet it lacks the characteristic scale of psoriasis and , in contrast to eczema,exhibits a sharp border. Ulcers on the lower extremities may signify BCC or squamous cell carcinoma. [29]

It's crucial to use a combination of direct inspection, dermoscopic examination, and histological examination for diagnosing basal cell carcinomas. Although typical lesions can be identified through direct inspection based on clinical findings, dermoscopy enhances diagnostic accuracy for suspicious lesions. Ultimately, a skin biopsy is essential for confirming the diagnosis and assessing the risk of recurrence. Histopathologically, basal cell carcinomas typically exhibit a proliferation of uniform, basaloid cells with hyperchromatic nuclei and limited, poorly defined cytoplasm, resembling epidermal basal cell morphologically but behaving akin to follicular germinative cells.[11]

Treatment:

- Surgical:

Mohs micrographic surgery (MMS):-

Mohs micrographic surgery indeed involves staged resection and thorough margin examination,leading to high cure rates,especially for high-risk lesions. This technique,typically used for facial lesions,aims to identify and excise all traces of infiltrating basal cell carcinoma (BCC) for complete cure while preserving normal tissues to the maximum extent.[1]

In the study of risk of developing another basal cell carcinoma, 1000 patients who underwent Mohs histographically controlled surgery for basal cell carcinoma were monitored over a period of 5 years, for the first 18 months, total boady skin examinations were conducted every 6 months, followed by yearly intervals. During these examination , any suspicious skin lesions were subjected to biopsy. The collected biopsy specimens underwent routine pathologic examination, and only those identified by pathologist as basal cell carcinoma were recorded as instances of skin cancer.[29]

To classify a case of second skin cancer, it was required that the site of the biopsy for the second

occurrence differed from the site of the biopsy for initial diagnosis. This criterion was likely implemented to distinguish independent occurrences of basal cell carcinoma rather than recurrence at the same site. The study aimed to track and analyzed the development of new cases of basal cell carcinoma among the patients over the follow-up period.[29]

- Curettage and cautery:-

Curettage and cautery,also known as electrodesiccation and curettage,as well as curettage alone,are traditional methods for basal cell carcinoma (BCC) removal.Success largely depends on the careful selection of appropriate lesions,ideally small nodular or superficial ones,and the skill of the operator. While suitable of low-risk lesions,curettage and cautery pose a higher risk of tumor recurrence for high-risk facial lesions,making it generally contraindicated in such cases.[1]

- Cryosurgery:-

Liquid nitrogen cryosurgery for basal cell carcinoma(BCC) relies on entreme cold(tissue temperatures of -50 to -60 C)to achieve deep destruction of the tumor and surrounding tissues.Techniquesvary,including open and closed spray methods,along with single or multiple freeze/thaw cycles. Double freeze/thaw cycles are typically recommended for ficialBCC,while superficial truncal lesions may require only a single cycle .Some reports mention 'fractional cryosurgery'for large lesions treated on separate occasions. Successful cryosurgery depends on the careful selection of lesions and the operator's experience.[1]

- Non-surgical:

Radiotheraphy-:Radiotheraphy (RT) proves effective in treating primary basal cell carcinoma (BCC),surgically recurrent BCC, and as adjuvant therapy.It is often considered the treatment of choice for high-risk disease in patients unwilling or unable to undergo surgery.The complex mix of techniques includes superficial RT for shallow lesions,electron beam therapy for deeper tissues,and brachytherapy for curved surface. While the equipment can be expensive,RT is typically available at major hospital centers. Modern techniques have reduced the likelihood of poor long-term cosmetics results,making it a viable option in various scenarios.[1]

Topical immunotherapy with Imiquimod:- Imiquimod (IMQ) is an immune response modifier that acts through toll-like receptors,primarily expressed on dendritic cells and monocytes.It includes the production of cytokines and chemokines, promoting both innate and adaptive cell-mediated immune responses. Studies have shown the efficacy of topical 5% IMQ cream in treating superficial basal cell carcinoma (sBCC). Dose-response studies suggest higher response rates with more frequent or prolonged dosing and a significant inflammatory reaction.The European Medicines Agency has approved topical IMQ for the treatment of small sBCC, using a 5X/week regimen for 6 weeks.[1]

Photodynamic therapy:-Previous guidelines from the British Associated of Dermatologists (BAD) have rated topical photodynamic therapy(PDT) using ALA as suitable for treating low-risk superficial basal cell carcinoma (sBCC) but considered it a relatively poor option for high-risk lesions.Studies comparing ALA-PDT with cryosurgery showed clinical recurrence rates at 12 months, with underestimates as histology revealed residual BCC in a percentage of cases for both treatments,raising concerns about the reliability of clinical observation for tumor clearance and the long-term efficacy of PDT. Further studies on double-cycle ALA-PDT reported initial high clearance rates for sBCC, with varying recurrence rates after 12 months of follow-up. A multicenter study on patients at high risk reported histologically confirmed initial clearance rates for both sBCC and nodular BCC (nBCC) following MAL-PDT treatment,with subsequent recurrence rates after 24 months .[1]

CONCLUSION

Basal cell carcinoma (BCC) is the most common type of skin cancer, characterized by slow growth and originating from basal cells. It frequently occurs on sun-exposed areas such as the face and neck, manifesting as pearly bumps, scars, or red patches. While BCC rarely metastasizes, untreated cases may invade surroundind tissues. Risk factors include prolonged sun exposure and fair skin.

Diagnosis involves a biopsy, a procedure where a small tissue sample is examined to confirm the presence of cancerous cells. Treatment options for BCC vary and can include surgical procedures to remove the tumor or topical medications for certain cases.

Prevention is crucial, with an emphasis on sun protection measures like sunscreen, protective clothing, and avoiding excessive sun exposure. Regular skin checks are essential for early detection, facilitatinf more effective management and reducing the risk of complications associated with untreated BCC. If any suspicious changes in the skin are noticed, seeking prompt medical evaluation is advisable for timely intervention and appropriate care.

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