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Journal of Skin and Sexually Transmitted Diseases

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Review Article

Basal cell carcinoma – Pathology

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Received: 25 April 2022
Accepted: 17 May 2022
EPub Ahead of Print: 27 June 2022
Published: 14 October 2022

DOI
10.25259/JSSTD_21_2022

Quick Response Code:

ABSTRACT

Basal cell carcinoma (BCC) that originates from the basal cells of the interfollicular epidermis and/or hair follicle is a locally aggressive neoplasm. The mutations that activate the hedgehog signaling pathway play an important pathogenic role. BCC can also occur in conjunction with familial cancer syndromes. A better understanding of the intricate molecular pathogenesis has opened up therapeutic options that are found useful in patients with aggressive or metastatic BCC. Apart from the morphological features, histopathology is crucial in assessing the prognosis of BCC and deciding the best treatment option.

Keywords: Basal cell carcinoma, Pathogenesis, Histopathology, Prognosis, Hedgehog signaling pathway

INTRODUCTION

Basal cell carcinoma (BCC) arises from the interfollicular epidermis and/or the hair follicle and shows a predilection for sun-damaged skin.[1] Mucous membranes, palms, and soles are rarely affected.[1-3] Disturbances in hedgehog pathway signaling induced by the removal of patched homolog 1 gene or activation of Smoothened proteins play a major role in the pathogenesis of BCC.[1,4] Histological classification helps to assess the prognosis and decide the treatment.[1-3,5]

The World Health Organization category for skin tumors 2018 has included BCC under keratinocyte malignancy and recognized BCC with sarcomatoid differentiation as a new histological variant.[2,3]

Table 1 shows the clinical variants and clinical mimics of BCC.[1,5-8]

HISTOLOGY

At low-power magnification, BCC appears as a basaloid epithelial tumor arising from the epidermis [Figure 1].[3] The basaloid epithelium forms a palisade. A cleft formation is seen between tumor nests and stroma which is referred to as retraction artifact [Figure 1].[3] Retraction artifact was attributed to mucin shrinkage occurring during fixation and staining of the specimen; however, in a recent paper, Mentzel *et al.* suggested the possibility of extracellular matrix degradation (that occurs during tumor growth), leading to the formation of retraction artifact.[9] The tumor shows centrally located nuclei, which are crowded with scattered, mitotic figures, and necrotic bodies. The presence of a mucinous stroma distinguishes BCC from other basaloid tumors arising from the skin. Occasionally, BCC shows areas of eosinophilic stroma. Infrequently, tumor stroma shows amyloid deposition.[3,5]

Table 1: Clinical variants and clinical mimics of BCC.

Clinical type	Morphology	Differential diagnosis
Nodular BCC (50–80%)	Common site is head and neck, manifests as a well-demarcated, pearly, shiny, papule or nodule, with scaling, smooth surface, rolled borders, and telangiectasia (arborizing and small telangiectasia), ulceration may occur (rodent ulcer)	Papule/nodule: Molluscum contagiosum, intradermal melanocytic nevus, seborrheic keratosis, trichoepithelioma, amelanotic melanoma, sebaceous hyperplasia, dermatofibroma, Merkel cell carcinoma, microcystic adnexal carcinoma, sarcoidosis, rosacea, fibrous papule of the nose Ulcerated lesion: Keratoacanthoma, squamous cell carcinoma
Superficial BCC (10–30%)	Affects relatively younger individuals, commonly seen on trunk and extremities, appears as a well-circumscribed, scaly, pink macule, papule, or a thin plaque with central clearing and a thin, rolled border, may show spontaneous regression, resolved lesions appear atrophic and hypopigmented	Psoriasis, actinic keratosis, Bowen's disease, nummular dermatitis, early amelanotic melanoma, and Paget's disease
Morphoeaform BCC (<10%)	Preferentially affects head and neck, indurated, elevated or depressed locally destructive plaque with a smooth, shiny, ivory white surface and ill-defined edges, aggressive type of BCC	Morphea, scar, Merkel cell carcinoma, dermatofibrosarcoma protuberans, amelanotic melanoma, trichoepithelioma, microcystic adnexal carcinoma
Infiltrative BCC	Poorly defined, indurated, flat or depressed plaque, that appears white, yellow, or pale pink in color, the overlying skin may show crusting, papules, erosion, and ulceration	Actinic keratosis, Bowen's disease, nummular dermatitis
Pigmented BCC	Nodular or superficial BCC with pigmentation	Malignant melanoma, appendageal tumor, compound nevus, blue nevus, and Spitz-Reed nevus
Fibroepithelial BCC (fibroepithelioma of Pinkus)	Common site is trunk, manifests as a flesh-colored or erythematous, sessile plaque, pedunculated papule or nodule	Skin tag, papillomatous dermal nevus, fibroma, and non-pigmented seborrheic keratosis
Infundibulocystic BCC	Seen in elderly, common sites are head and neck, manifests as well circumscribed, pearly, papules	Benign follicular adnexal processes

BCC: Basal cell carcinoma

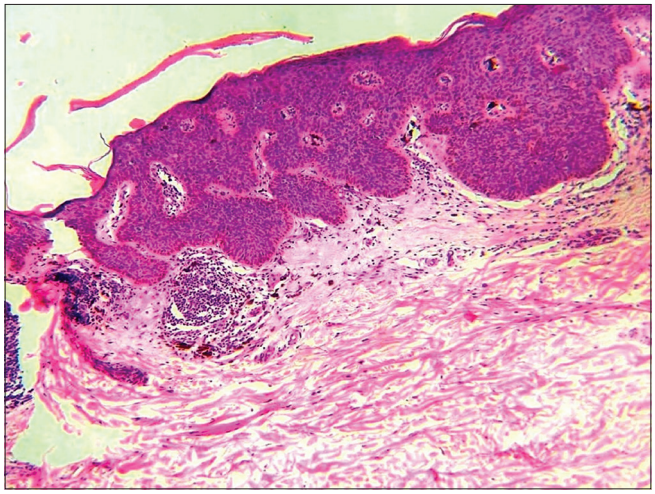

Figure 1: Basal cell carcinoma of skin arising from the basal layer of epidermis and arranged as islands of basaloid cells of variable size and shape with jagged contours (H and E, ×200).

In 1978, Wade and Ackerman categorized BCC into 26 histopathological types.[10] The histopathological classification is based on the histological growth pattern and the differentiation. Maximum prognostic significance is assigned to the growth pattern. The histological growth pattern is taken into consideration while categorizing BCC as low-risk and high-risk types.[11-13]

In the following section, the different histological subtypes are discussed. In Table 2, the histological differential diagnoses of each type are given.[14]

Nodular BCC

Nodular BCC appears as a circumscribed mass. Large tumor nodules extending deep into the dermis is the characteristic histology finding. Ulceration is a common feature of large lesions, which had earned the tumor the historical term "rodent ulcer" [Figure 2]. Epidermal or follicular attachment is a common finding. The tumor shows large basaloid lobules. The lobules manifest peripheral nuclear palisading. The central portion of the lobule may be solid or cystic (due to excessive mucin production). Fibromyxoid stroma surrounds the tumor islands with cleft formation between the tumor and the stroma. Other features include

Table 2: Histological differential diagnoses of basal cell carcinoma and differentiating features.

The histological variant of basal cell carcinoma	Histological differential diagnosis	Differentiating features
Superficial BCC	Follicular induction (follicular basal cell hyperplasia, epidermal basaloid cell hyperplasia, and basaloid epidermal proliferation)	Follicular induction is seen above a dermatofibroma or less commonly above a nevus. It shows clear cell hyperplasia and epidermal hyperplasia between the sites of follicular induction.
	Tumor of follicular infundibulum	Tumor of follicular infundibulum shows conspicuous basement membrane and cytoplasmic pallor (due to glycogen). The tumor lacks cytologic atypia, mitotic activity, myxoid inflammatory stroma, and tumor-stroma clefting. Other distinguishing features include colonizing Merkel cells (cytokeratin 20 positive) and an elastin fiber network at the base of the lesion.
	Actinic keratosis	BCC cells are BerEP4 positive.
Nodular BCC	Nodular BCC with focal micronodular architecture	Stroma encases nodular BCC. The satellite pattern (as seen in nodular BCC with focal micronodular architecture) is missing.
Sclerosing/ morphoeic BCC	Desmoplastic trichoepithelioma	Desmoplastic trichoepithelioma does not extend into the deep dermis. It shows architectural symmetry, horn cysts with calcification, and granulomatous inflammation. PHLDA1+ cells are highly specific for trichoepithelioma/trichoblastoma. No single immunohistochemistry marker can differentiate between trichoepithelioma and BCC. Stromal fibroblasts of BCC (but not trichoepithelioma) show positive staining for fibroblast activation protein.
	Microcystic adnexal carcinoma	Microcystic adnexal carcinoma shows no peripheral palisading, mitotic activity, tumor-stroma clefting, or myxoinflammatory stroma. BCC cells are BerEP4 positive.
Basosquamous carcinoma	Basaloid SCC	BCC cells are BerEP4 positive and epithelial membrane antigen negative. SCC cells are BerEP4 negative and epithelial membrane antigen positive.
	Collision tumor of BCC and SCC	Collision tumor of BCC and SCC shows the presence of both malignancies with a clear delineation of each tumor.
Pigmented BCC	Malignant melanoma	Malignant melanoma lacks basaloid islands and show HMB-45 and Melan-A positive cells.
	Pigmented seborrheic keratosis	Pigmented seborrheic keratosis shows proliferation of basaloid keratinocytes without atypia in the epidermis. It shows acanthosis and hyperkeratosis, most often associated with pseudo-horn cysts.
BCC with adnexal differentiation	Basaloid follicular hamartoma	Basaloid follicular hamartoma shows cystic structures which are uncommon in BCC, except for the infundibulocystic type. Tumor necrosis, mitotic activity, cytologic atypia, myxoinflammatory stroma, and peripheral clefting differentiate BCC from basaloid follicular hamartoma. Basaloid follicular hamartoma cells are CD34 positive (outlines tumor islands).
	Trichoepithelioma	Retention of cytokeratin 20+ve Merkel cells is seen in appendage tumors, but not in BCC. Tumor cells of BCC are Bcl2 and CD10 positive, a reverse pattern staining is seen in the stromal cells of trichoepithelioma.
	Sebaceous carcinoma	Sebaceous carcinoma shows intraepidermal pagetoid spread, sebaceous, lobular architecture, greater cytologic atypia, and less basaloid morphology, cells of sebaceous carcinoma show diffuse staining with diffuse androgen receptor, while BCC cells show focal positivity, sebaceous carcinoma cells are low-molecular-weight cytokeratin, epithelial membrane antigen, adipophilin, and perilipin positive and BerEP4 negative.
	Polymorphous sweat gland carcinoma	Polymorphous sweat gland carcinoma cells show strong positivity for pancytokeratin, cytokeratin5/6, p40, p63, and p16.
Fibroepithelial BCC	Eccrine syringofibroadenoma	Eccrine syringofibroadenoma is predominantly seen on the extremities and histology shows anastomosing cords of pale cuboidal cells that extend from epidermis into the dermis; these strands show tubular structures, resembling eccrine ducts.

BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, HMB-45: Human melanoma black 45.

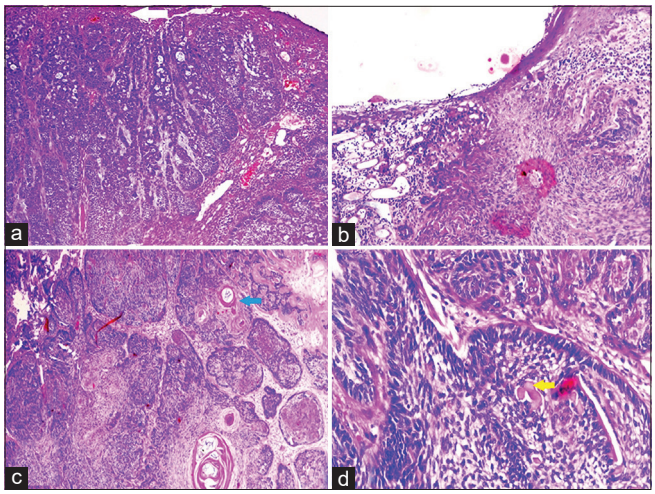

Figure 2(a): Nodular basal cell carcinoma of skin showing tumor islands of varying sizes in the dermis (H and E, ×40); (b): ulceration in the epidermis, and cystic, and diffuse areas in the subepidermal region (H and E, ×40); (c): tumor islands with keratin pearls (blue arrow, H and E, ×200); (d): islands with peripheral palisading of nuclei and eosinophilic amyloid stroma (yellow arrow, H and E, ×400).

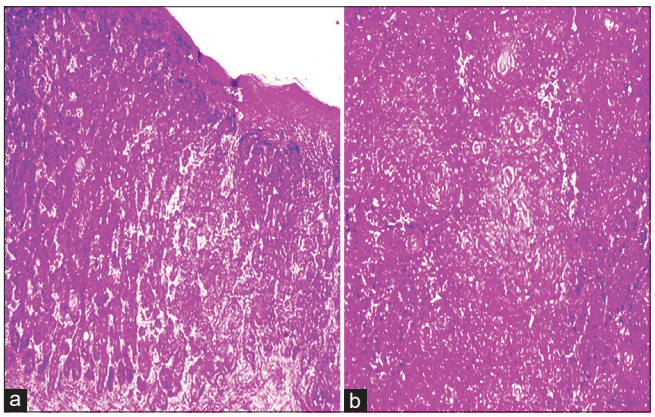

Figure 3(a): Nodular basal cell carcinoma of skin showing tumor islands of varying sizes in the dermis arising from the basal layer and extending widely throughout the dermis (H and E, ×100); (b): tumor islands show areas of keratinization (H and E, ×200).

mild pleomorphism, variable mitotic activity, apoptosis, and occasional necrosis.[2,3,5] Nodular BCC is further classified into keratotic [Figure 3], nodulocystic [Figure 4], and adenoid types.[2,3,5,11]

Micronodular BCC

More than 50% of the tumor is composed of small, discrete nodules, each <0.15 mm in diameter.[2,3] The micronodules are separated by normal dermal collagen, giving the appearance of separate satellites outlined by a thin rim of stroma.[2,3,5] Small basaloid nests that deeply and diffusely infiltrate the dermis and extend into the subcutis characterize this BCC variant.[2,3,5] A less marked peripheral palisading and absence of retraction artifact are distinguishing features of micronodular BCC.[2,3,5]

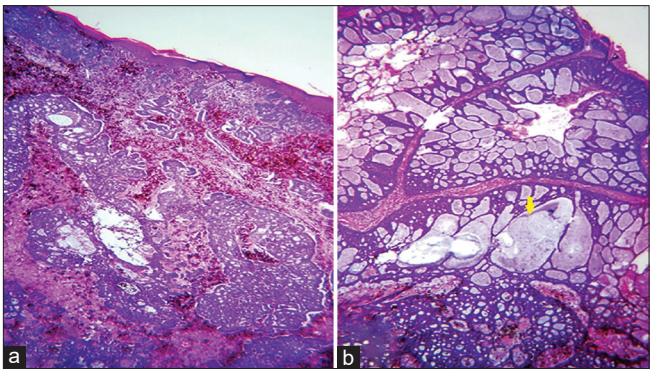

Figure 4(a): Nodulocystic basal cell carcinoma of skin composed of large basaloid lobules with solid and cystic areas due to excessive mucin production and fibromyxoid stroma (H and E, ×100); (b): yellow arrow indicates cystic spaces with mucin (H and E, ×200).

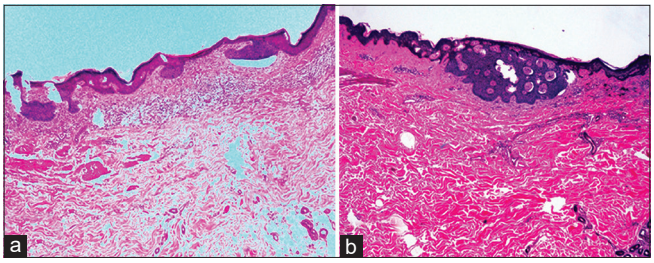

Figure 5(a): Superficial basal cell carcinoma multicentric (H and E, ×40); (b): Superficial basal cell carcinoma unicentric, exhibiting buds and irregular proliferation of tumor cells attached to an atrophic epidermis, and showing little penetration into the dermis (H and E, ×100).

Superficial BCC

Histologically, superficial BCC appears as isolated basaloid lobules extending from the lower margin of the epidermis [Figure 5]. The tumor is <1 mm thick and does not extend beyond the papillary dermis.[2,5] Occasionally, superficial BCC can appear as part of a mixed pattern tumor with nodular, micronodular, or infiltrating components.[5]

Pigmented BCC

Pigmented BCC shows an increased number of benign dendritic melanocytes within the tumor islands and phagocytosed melanin within the tumor cells and peritumoral macrophages [Figures 6a and b]. Pigmented BCC is considered as a variant of nodular or superficial BCC since the mentioned changes may be observed in either of the two.[5]

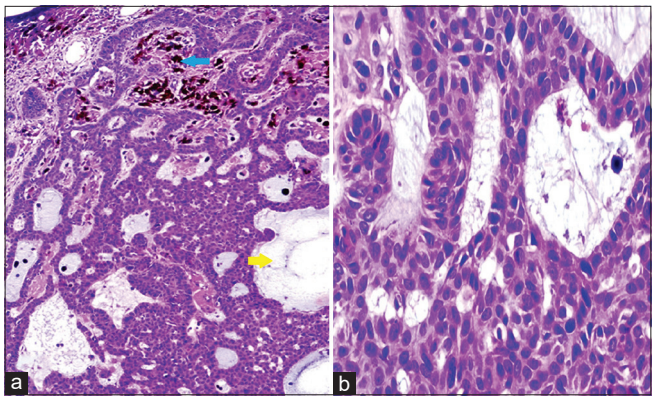

Figure 6(a): Pigmented basal cell carcinoma nodular variant showing melanophages (blue arrow) and mucin (yellow arrow) in the stroma of tumor (H and E, ×200); (b): colonization of tumor nests with melanocytes (H and E, ×400).

Infiltrating BCC

Infiltrating BCC, also known as BCC with aggressive growth pattern, shows more than 5–8 cell thick, tumor nests.[2,3,5,11] Narrow tumor cords and nests with irregular, infiltrative growth patterns characterize the histology picture. Nearly one-third of cases of infiltrating BCC are admixed with nodular BCC. A frequent finding is perineural invasion which overlaps with morphoeic/sclerosing BCC.[2,3,5] Infiltrating BCC is associated with a high risk of recurrence.[2,3]

Sclerosing/morphoeic BCC

Disruption of normal dermal architecture by very thin narrow cords (1–5 cell thick) of basaloid cells which are compressed by abundant sclerotic collagenous stroma marks sclerosing/morphoeic BCC. The tumor forms an irregular/tentacular, deeply infiltrative border with the surrounding stroma.[2,3] The retraction artifact is seldom seen. The presence of a highly collagenous stroma differentiates sclerosing BCC from the infiltrating variant.[5]

Sclerosing BCC frequently manifests perineural invasion and has a high rate of recurrence. This high-risk BCC warrants surgical excision with strict margin control.[2,3]

Basosquamous carcinoma

Basosquamous or metatypical carcinoma shows the histological features of both squamous cell carcinoma (SCC) and BCC and a transition zone between the two.[2,3,5] Islands of basaloid cells are seen admixed with atypical squamous cells. The atypical squamous cells with abundant eosinophilic cytoplasm are seen focally or scattered throughout. Cells with features that are intermediate between SCC and BCC constitute the transition zone. The highly cellular stroma appears fibrotic.[5] Perineural invasion (10%), local recurrence (4.5%), and lymph node metastasis (5%) are seen less frequently.[2,3]

BCC with sarcomatoid differentiation

BCC with sarcomatoid differentiation is also known as metaplastic carcinoma, sarcomatoid BCC, or carcinosarcomatous BCC.[2,3] The tumor shows a basaloid epithelial component and a sarcomatous stroma, which can exhibit a variety of histology patterns.[2,3,5] The malignant mesenchymal stroma can appear as pleomorphic undifferentiated sarcoma, osteosarcoma, chondrosarcoma, leiomyosarcoma, or rhabdomyosarcoma.[2,3,5] The prognosis remains unclear due to scarcity of information regarding this rare variant.[2,3]

BCC with adnexal differentiation

This BCC variant commonly affects periocular skin. BCC with adnexal differentiation may differentiate toward follicular, sebaceous, apocrine, or eccrine glands.[2,3,10,11] The characteristic features of different subtypes of BCC with adnexal differentiation are given below:

1. BCC with matrical differentiation shows shadow cells with hair matrix differentiation.[2,3,5]
2. Infundibulocystic BCC shows differentiation toward the follicular infundibulum with anastomosing cords and nests of basaloid cells, punctuated by small infundibular cyst-like structures.[2,3,5]
3. BCC with sebaceous differentiation shows mature sebocytes which stain positive for epithelial membrane antigen (EMA).[2,3,5]
4. BCC with ductal differentiation manifests ducts resembling those seen in apocrine (with decapitation secretion) and eccrine (ducts with a distinct cuticle) glands. These cells stain positively for carcinoembryonic antigen (CEA) and EMA.[2,3,5]

Multiple infundibulocystic BCC and BCC with sebaceous differentiation are seen in nevoid BCC syndrome and Muir –Torre syndrome, respectively.[3,4]

Fibroepithelial BCC

Fibroepithelial BCC is also known as fibroepithelioma of Pinkus or Pinkus tumor. It is composed of delicate, interanastomosing strands of basaloid cells extending downward from the epidermis. Abundant fibroblastic stroma surrounds the tumor strands. Basaloid islands are rarely seen.[2,3,5]

IMMUNOHISTOCHEMISTRY (IHC)

IHC is very useful in distinguishing BCC from other basaloid tumors such as trichoepithelioma and basaloid

Table 3: Histological subtyping of basal cell carcinoma (BCC) stratified by risk of recurrence.

Lower risk	Higher risk
Nodular BCC	Basosquamous BCC
Superficial BCC	Sclerosing/morphoeic BCC
Pigmented BCC	Infiltrating BCC
Infundibulocystic BCC	BCC with sarcomatoid differentiation
Fibroepithelial BCC	Micronodular BCC

SCC. Small biopsy, mishandling of specimen, crushing of tissue beyond recognition, and excess drying or poor fixation can make it difficult to appreciate the histology features. In such instances, IHC serves as an important diagnostic tool.[2,3]

BCC tumor cells are pancytokeratin (100%), BerEP4 (80–100%), p63 (100%), CAM5.2 (20–95%), androgen receptor (33–66%), p53 (74.5–83%), 34 beta E12 (high-molecular-weight cytokeratin), Bcl2 (diffuse pattern staining), and CD10 (positive in tumor cells and negative in stroma) positive and cytokeratin 20, adipophilin, SOX10, S100, Melan A/MART1, human melanoma black-45, CD34, and CD44 negative.[13-17]

PROGNOSIS

TNM staging is rarely reported for BCC since it mostly remains a localized neoplasm. The National Comprehensive Cancer Network guidelines stratify BCC variants as those with a low and a high risk of recurrence.[1,2,11,13]

Tumor prognosis based on histopathology features

Primary superficial BCC, primary nodular BCC of <1 cm size in an intermediate-risk location (forehead, cheeks, chin, neck, and scalp), and primary nodular BCC of <2 cm size in a low-risk location (trunk and limbs) are associated with good prognosis.[2]

An intermediate prognosis is associated with recurrent superficial BCC and nodular BCC of <1 cm size in a high-risk location (centrofacial areas, nose, ears, periorificial areas, and embryonic fusion planes), <2 cm size in an intermediate-risk location, and >2 cm size in a low-risk location.[2]

A poor prognosis is assigned to nodular BCC of >1 cm size in a high-risk location, which shows a high risk of recurrence. Morpheaform, infiltrative, or histologically aggressive BCC, and recurrent BCC except superficial BCC are associated with a very high risk of recurrence.[2] Other histologic prognostic indicators include perineural and lymphovascular invasion and status of surgical margins.[2,13-17] Table 3 shows the recurrence risk associated with histological variants of BCC.[2,17]

CONCLUSION

Histopathology findings have diagnostic, prognostic and therapeutic significance in BCC.

Declaration of patient consent

Not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Balakrishnan S. Basal cell carcinoma – Pathology. J Skin Sex Transm Dis 2022;4:164-70.