

Educational Case: Basal Cell Carcinoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289521998030>.¹

Keywords

pathology competencies, organ system pathology, skin, malignant skin neoplasms, basal cell carcinoma

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Primary Objective

Objective SK5.2: Malignant Skin Neoplasms: Describe the clinical presentation, precursor lesions, risk factors and hereditary cancer syndromes that lead to the following skin cancers: basal cell carcinomas, squamous cell carcinoma, and melanoma.

Competency 2: Organ System Pathology; Topic: Skin (SK); Learning Goal 5: Skin Neoplasia

Patient Presentation

A 64-year-old white man presents to his primary care provider with a chief concern of several bleeding bumps on his neck and forehead. He recently retired from a long career in landscaping. He states that the bumps have grown slowly over the past 2 years. The bumps are painless; however, they have begun to bother him as they frequently bleed with the slightest touch. He notes that the bumps are itchy at times. He originally suspected the bumps to be insect bites as he frequently spends time outdoors, but they do not seem to heal. He has attempted both calamine lotion and creams containing hydrocortisone but neither have provided relief or resolution. Past medical history is significant for a supracondylar fracture from a bicycle accident and dyslipidemia. The patient's only medication is atorvastatin.

Diagnostic Findings: Part I

Physical examination is notable for a white man with fair skin and blue eyes. Several lesions are present including a pearly

papule with fine telangiectatic vessels measuring 1.4 cm in size on the anterolateral neck, a nodular papule with rolled, waxy borders and ulceration measuring 1.7 cm in size on the superolateral forehead, and a flesh-colored nodule measuring 0.8 cm in size on the infraorbital margin (Figure 1). The facial skin is leathery with deep forehead wrinkling. The back of the neck has significant creasing with a leathery texture.

Question/Discussion Points, Part I

What Is the Differential Diagnosis Based on the Clinical Presentation?

The patient is presenting with multiple papules and nodules suspicious for malignant neoplasms of the skin. The differential diagnosis would include nodular basal cell carcinoma (BCC), sebaceous hyperplasia, nonpigmented nevus, fibrous papule, squamous cell carcinoma (SCC), and keratoacanthoma. Given the patient's history of a career in landscaping, fair, leathery skin, blue eyes, extensive wrinkling, and evidence of cutis rhomboidalis nuchae on physical examination, a diagnosis of BCC is at the top of the differential.

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Figure 1. The nodular lesion has a waxy (pearly) appearance with rolled borders, central ulceration, and telangiectasias at the periphery.

Clinically, How Do Melanoma and Squamous Cell Carcinoma Differ From Basal Cell Carcinoma?

Both BCC and SCC are keratinocyte carcinomas and are often referred to as nonmelanoma skin cancer (NMSC). Unlike BCC and SCC, melanoma is a cancerous neoplasm of pigment-forming cells—melanocytes. Melanoma carries a much higher morbidity and mortality and thus, it is important to rule out.

Clinically, the superficial variant of BCC may resemble early forms of melanoma.² Melanoma is most commonly identified clinically by using the ABCDE mnemonic—*asymmetry, irregular borders, color variation, diameter* ≥ 6 mm, and *evolution* over time.

The most characteristic feature of BCC is a waxy, pink, pearly appearance. These lesions often contain prominent subepidermal blood vessels (telangiectasia) as well as ulceration.² It is important to note that BCCs are seen almost exclusively on hair-bearing skin, especially on the face. It is very rare for a BCC to arise on the lower extremities.³ Clinically, SCC can be recognized as a scaling, indurated plaque. Squamous cell carcinoma may arise from a preexisting actinic keratosis or *de novo*. While both BCC and SCC are most often found on sun-exposed areas, it is interesting to note that BCC is more common on the upper lip while SCC is more common on the lower lip.⁴ Additionally, patients with a BCC or SCC may report easy bleeding of the skin lesion, whereas, this feature is rarely present in melanoma.

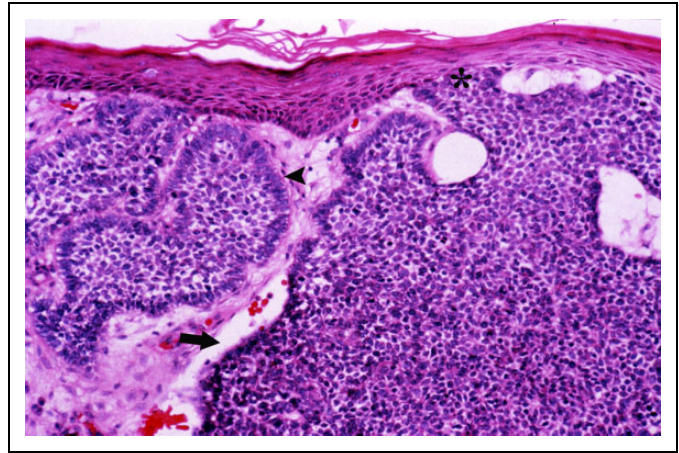


Figure 2. Arising from the basal layer of the epidermis (*) are islands of basophilic tumor cells that extend into the dermis that has a loose mucinous consistency. Peripheral palisading of the nuclei (arrowhead) accompanied by retraction artifact (clefing; arrow) is characteristic. (H&E, intermediate power).

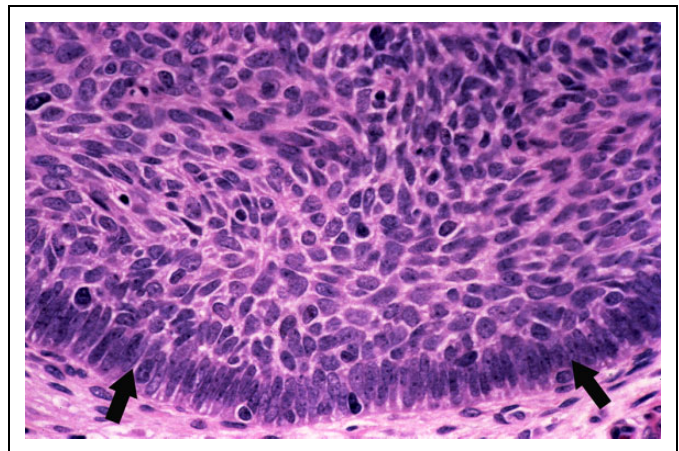


Figure 3. Palisading of the basophilic tumor cells with hyperchromatic nuclei (picket fence pattern) at the junction between the tumor cells and dermis is present (arrows). (H&E, intermediate power).

Diagnostic Findings: Part 2

Three skin biopsies are performed. Histological features of the cutaneous biopsies are shown in Figures 2 and 3.

Question/Discussion Points, Part 2

Describe the Histological Features Observed in the Biopsies?

The biopsies show islands of basaloid cells extending from the epidermis into the dermis. The basophilic tumor cells have hyperchromatic nuclei with increased number of mitoses surrounded by a loose stroma. There is palisading of the peripheral layer of cells characterized by parallel alignment of the long axis of the nucleus.

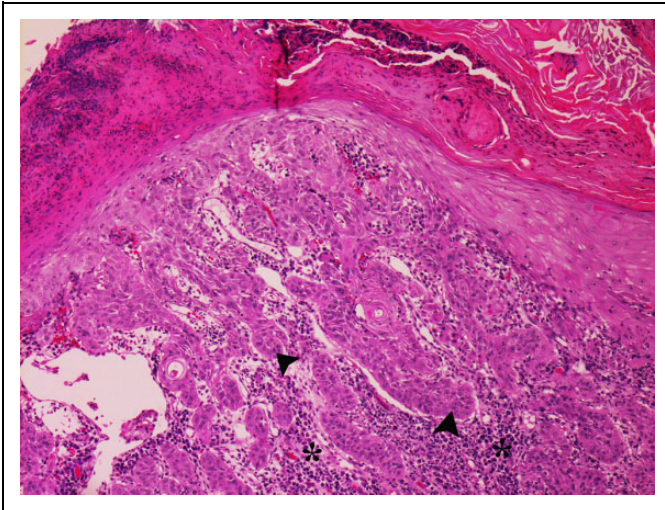


Figure 4. Islands of keratinocytes arising from the epidermis (arrowheads) extend into the dermis. The pleomorphic tumor cells have prominent nucleoli with increased mitotic rate. Surrounding the tumor cells is a prominent chronic inflammatory infiltrate (*). (H&E, intermediate power).

Based on the Biopsy Findings, What Is the Diagnosis?

Biopsy findings are consistent with a diagnosis of BCC. Basal cell carcinoma is the most common human malignant disease and the incidence continues to rise. In the United States, the lifetime risk is estimated to be >20%.⁵ The mortality associated with BCC is low. However, significant morbidity may result following local tumor destruction.⁶

What Are the Histologic Features of Basal Cell Carcinoma?

Basal cell carcinoma is identified by uniform islands and/or cords of basaloid cells arising from the basal layer of the epidermis on histological examination. Peripheral palisading is present around the rim of tumor islands. Stromal separation artifact (known as clefting or retraction) is common following sectioning of the tumor (Figures 2 and 3). This feature is helpful in differentiating BCC from other tumors which involve proliferation of basaloid cells.² Hyperchromatic nuclei are also present, along with apoptotic bodies. Amyloid may be present in the stroma, commonly at the advancing edge.³

How Do Melanoma and Squamous Cell Carcinoma Differ From Basal Cell Carcinoma Morphologically?

In SCC, malignant keratinocytes disrupt the dermoepidermal junction (Figure 4). Squamous cell carcinoma has varying degrees of differentiation ranging from well to poorly differentiated.⁷ Tumors are graded based on the least differentiated element.³ Mitoses are often absent or rare.⁷ Heavy inflammatory infiltrate, usually composed of T lymphocytes, often accompanies the tumor.³ Furthermore, similar to BCC, there

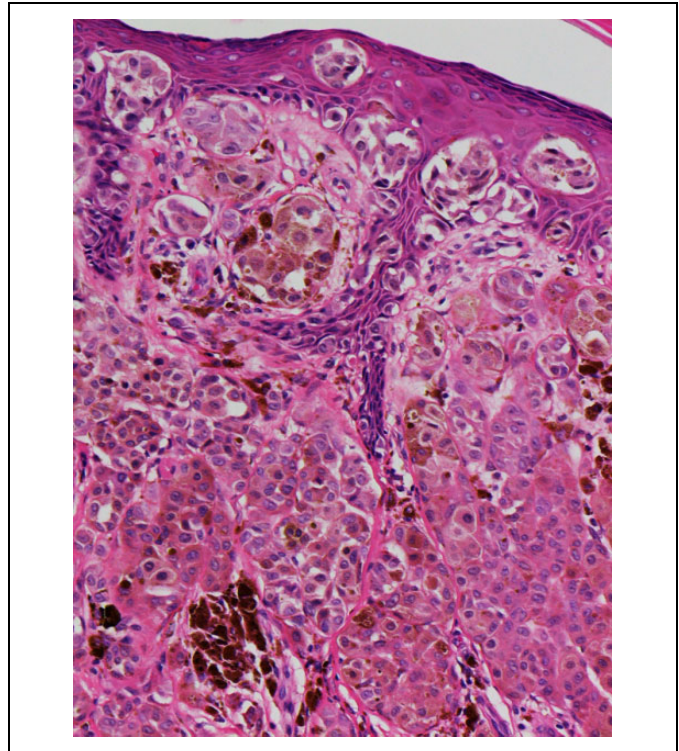


Figure 5. Nests of pleomorphic pigmented melanocytes with prominent nucleoli are present throughout the dermis and within the epidermis. (H&E, intermediate power).

are a number of histologic variants, some carrying a higher risk than others.³

Four major subtypes of melanoma are recognized—superficial spreading, lentigo maligna, nodular, and acral lentiginous melanoma.³ Melanoma exhibits either a radial or horizontal growth phase. In radial growth, irregular nested and single growth of melanoma cells are confined to the epidermis or superficial dermis² (Figure 5). This is accompanied by an inflammatory response in the dermis.² Following a radial growth phase, melanoma shifts into the vertical growth phase, where cohesive nests of infiltrating cells invade deeper into the dermal layers.² At this point, the melanoma gains the capacity for lymphovascular invasion and metastatic spread.³ Mitotic figures are common.³

What Are the Predisposing Factors for Basal Cell Carcinoma?

The most common risk factor for BCC is ultraviolet (UV) exposure, specifically UVB. Although prolonged exposure to sunlight is an important cause, that alone is not sufficient to produce BCC. There is a higher incidence of BCC in light skinned individuals of Northern European descent. A history of blistering sunburns in childhood, excessive recreational exposure to UV in the first 2 decades of life, tanning bed use, and close proximity to the equator is not uncommon.^{3,8} However, several other factors may increase one's risk including

Table 1. Gross and Histologic Features of Basal Cell Carcinoma Subtypes.^{3,5,8,13}

Subtype	Gross features	Histologic features
Nodular/ Ulcerative	Pearly papules or nodules with arborizing telangiectasia, ulceration develops over time, sharply demarcated with a rolled border, most common on head and neck	Well-demarcated nests of basaloid cells, peripheral palisading, cystic change with central tumor necrosis possible, stromal retraction
Superficial	Slowly enlarging, scaly red patch, may include a thin, translucent, rolled border, can be mistaken for eczema or psoriasis, most common on trunk	Interconnected basaloid nodules (may appear isolated) projecting from the lower margin of the epidermis
Infiltrative and morpheaform	Both with poorly demarcated clinical margins Infiltrative: indurated, flat, or depressed plaque, often with overlying crust, ulceration, or erosions Morpheaform: also called sclerosing, resembles morphea or localized scleroderma, pink to ivory-white plaques, often shiny, smooth and scar-like, associated atrophy, most common on head and neck	Both rarely with palisading or retraction Infiltrative: nests of variable size with irregular, jagged borders, loose stroma, mucin often prominent Morpheaform: extensive sclerosis of the collagen with thick fibers and bundles, called “single filing,” often paler cells compared with other subtypes, surrounding stroma is dense, perineural invasion not uncommon
Pigmented	Pigment may be patchy or evenly dispersed, can be confused with melanoma or warts	Pigment is melanin from melanocytes within tumor nests, melanin seen both within the tumor and in surrounding dermis, hemosiderin may be evident

therapeutic ionizing radiation, arsenic exposure (via water, medication, or diet), immunosuppression, and transplants.⁸ Specifically, patients with HIV have a 2-fold higher incidence of BCC while transplant patients have a 5- to 10-fold higher incidence.⁹ Furthermore, BCC may arise from previous scars including but not limited to surgical and burn scars.³ Finally, a number of hereditary cancer syndromes, discussed below, are associated with BCC.

Describe the Pathogenesis of Basal Cell Carcinoma.

Mutations in the sonic hedgehog (SHH) pathway are associated with the development of BCC. Mutations in patched 1 (*PTCH1*) and, to a lesser degree, smoothed (*SMO*) genes account for the vast majority of BCC mutations.¹⁰ The most common mutation affects PTCH, a tumor suppressor protein, encoded by the *PTCH1* gene, allowing for the constitutive activation of the SHH pathway. This gene is on chromosome 9q22.3.² *SMO* is a 7-transmembrane protein, encoded by the *SMO* gene, located downstream of *PTCH1*.⁸ *SMO* mutations result in increased transcription of *GLI1*.^{2,8} Loss of function mutations in *SUFU*, a negative regulator of the SHH pathway, have also been identified.⁵ Thus far, 2 small molecule SHH inhibitors have been approved by the US Food and Drug Administration—vismodegib and sonidegib, for the treatment of locally advanced, recurrent, and metastatic BCC.¹¹ *TP53* mutations have also been identified.¹² Research into the pathways and genes causing BCC carcinogenesis is ongoing. An integration of clinicopathologic features with molecular genetics will be required to develop future BCC guidelines.¹⁰

What Are the Different Subtypes of Basal Cell Carcinomas? Describe the Gross and Histopathologic Features for Each.

The main subtypes of BCC outlined in Table 1 include nodular/ulcerative, pigmented, superficial (multifocal), infiltrative, and

morpheaform.^{3,5,8,13} Often, lesions exhibit more than one histopathologic pattern.⁵ The nodular/ulcerative subtype is the most common (45%-60%) followed by superficial (15%-35%), infiltrative and morpheaform (4%-17%), and pigmented (1%-7%).³

What Are the Complications of Basal Cell Carcinoma?

The vast majority of BCCs do not metastasize and have a relatively indolent course. However, metastasis is possible in lesions that have been neglected for many years. Large BCCs (>2 cm in diameter) have a higher risk of local recurrence, metastasis, and/or death compared to smaller tumors.¹⁴ Regional lymph nodes, lung, and bone are the most common sites of metastasis.¹⁵ Recurrence is also possible with an estimated rate of 12% at 10 years following standard surgical excision.¹⁶ Finally, patients with a prior history of BCC have a 10-fold increased risk for future skin cancers—both NMSC and melanoma.¹¹ Thus, patients should be screened with skin examinations every 6 to 12 months for the first 2 years following a diagnosis of BCC and then annually if no further skin cancer develops.¹¹

What Hereditary Cancer Syndromes Are Associated With Basal Cell Carcinoma?

Many hereditary cancer syndromes have been associated with BCC including nevoid basal cell carcinoma syndrome (NBCCS) also known as Gorlin or Gorlin-Goltz syndrome, Rombo syndrome, Bazex-Dupre-Christol syndrome, Brooke-Spiegler syndrome, Rothmund-Thomson syndrome, multiple hereditary infundibulocystic BCC, Schopf-Schultz-Passarge syndrome, the Dowling-Meara subtype of epidermolysis bullosa simplex, Werner syndrome, Bloom syndrome, and xeroderma pigmentosa.^{5,17}

Nevoid basal cell carcinoma syndrome is an autosomal dominant disorder resulting in numerous BCCs, often before

the second decade of life.² Patients with NBCCS have characteristic facial features and are susceptible to a wide variety of both benign and malignant neoplasms.¹⁷ Medulloblastomas and ovarian fibromas are examples. Nevoid basal cell carcinoma syndrome is associated with mutations involving the *PTCH1* gene (discussed above).²

What Are the Treatment Options for Basal Cell Carcinoma?

There are a number of different options available for treatment of BCC including standard surgical excision, curettage and electrodesiccation, radiation, cryotherapy, photodynamic therapy, Mohs micrographic surgery, laser therapy, and systemic and topical chemotherapy.¹⁵ Treatment is patient-specific and influenced by a number of factors including biopsy histopathology results, lesion location, size, comorbid conditions, primary tumors versus recurrence, and patient age. Risk stratification for BCC is done using the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).¹¹ Most often, standard surgical excision with a 4-mm margin or curettage and electrodesiccation is employed for low-risk BCC.⁵ For high-risk BCC, most providers treat with standard excision and a wider margin (>4 mm) or Mohs micrographic surgery.¹¹ A BCC is classified as high-risk histologically if there is perineural involvement. Additionally, several BCC subtypes are automatically labeled high-risk, these include micronodular, infiltrative, sclerosing, and morpheaform (or desmoplastic).¹¹

Teaching Points

- Basal cell carcinoma (BCC) is the most common human malignant disease; in the United States, the lifetime risk of BCC is >20%.
- Risk factors for BCC include ultraviolet light, a history of blistering sunburns in childhood, tanning bed use, therapeutic ionizing radiation, arsenic exposure, hereditary cancer syndromes, and immunosuppression.
- On histology, BCC characteristically includes islands of basaloid cells with peripheral palisading and hyperchromatic nuclei.
- Mutations in the sonic hedgehog pathway including patched 1 (*PTCH1*) and smoothened (*SMO*) genes are associated with BCC development. Mutations in *TP53* have also been identified.
- The main subtypes of BCC, in order of prevalence, include nodular/ulcerative, superficial, infiltrative, morpheaform, and pigmented (Table 1).
- In most cases, BCC exhibits an indolent course. However, neglected tumors do have the capacity to metastasize.
- Basal cell carcinomas are associated with a number of hereditary cancer syndromes, most notably nevoid basal cell carcinoma syndrome (NBCCS) also known as Gorlin-Goltz syndrome.
- Current treatment of BCC depends upon a variety of factors including lesion location and histopathologic features. Treatment options include standard surgical excision, curettage and electrodesiccation, radiation, cryotherapy, photodynamic therapy, Mohs micrographic surgery, laser therapy, and systemic and topical chemotherapy.

Authors' Note

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