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CE Credit - Topic Review

A Case of Mistaken Identity: Presumed Basal Cell Carcinoma Unmasked as Squamous Cell Carcinoma

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INTRODUCTION:

Basal cell carcinoma and squamous cell carcinoma are the most common malignant tumors of the eyelid. Although basal cell carcinoma is more common, squamous cell carcinoma can closely mimic its' appearance, highlighting the need for an accurate diagnosis to guide timely and appropriate management.

CASE REPORT:

A 66-year-old Caucasian male presented for a routine eye exam without complaints. He denied pain, discomfort, flashes, floaters, or double vision. His medical history included type II diabetes, hyperlipidemia, sleep apnea, and hypertension. Slit lamp examination of the right eye revealed a large (~5 mm), nodular lesion with ulceration on the temporal margin of the right upper lid. Given its size, ulceration, and reported progression, the lesion was initially suspected to be basal cell carcinoma, and the patient was referred to an oculoplastic surgeon with coordinated dermatologic care. Histopathologic analysis of a shaved biopsy revealed a well-differentiated squamous cell carcinoma extending to the deep margins of the specimen.

CONCLUSION:

This report reviews the epidemiology, clinical presentation, management, and treatment of basal cell carcinoma and squamous cell carcinoma of the eyelid and presents a case in which a lesion initially presumed to be basal cell carcinoma was ultimately identified as squamous cell carcinoma on histopathology.

Keywords: basal cell, carcinoma, eyelid, MOHs, squamous cell, ulceration

INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignant tumor of the eyelid. While it rarely metastasizes, it demonstrates locally invasive behavior that can cause functional deficits, permanent cosmetic concerns, and morbidity if left untreated. A diagnostic challenge is that BCC often appears deceptively benign, with lesions mimicking chalazion or papilloma, which can delay recognition and biopsy.

Squamous cell carcinoma (SCC), although less common than BCC in the periocular region, poses a greater risk due to its higher potential for recurrence, perineural invasion, and metastatic spread. Clinically, SCC may present with ulceration, crusting, or keratinization, yet in early stages it can resemble BCC, making differentiation based on clinical appearance alone difficult.

The case presented here illustrates this clinical challenge by describing a lesion initially presumed to be basal cell carcinoma that was ultimately diagnosed as squamous cell carcinoma.

CASE REPORT

A 66-year-old Caucasian male presented for a routine eye exam without complaints. He denied pain, discomfort, flashes, floaters, or double vision. His medical history included type II diabetes, hyperlipidemia, sleep apnea, and hypertension. Visual acuity was 20/20 in both eyes without correction and with best correction. Extraocular movements, confrontation visual fields, and pupils were normal. Slit lamp examination of the right eye revealed a large (~5 mm), nodular lesion with ulceration on the temporal margin of the right upper lid (Figure 1). The left

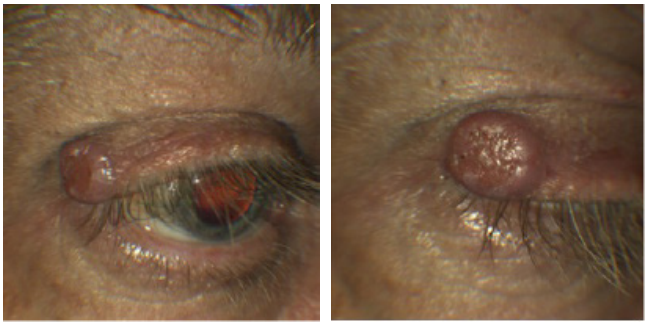

Figure 1: The right eyelid reveals a large, nodular lesion with ulceration on the temporal margin.

eye was unremarkable. Dilated fundus examination showed a normal posterior pole and periphery in both eyes. After further discussion, the patient stated he noticed this new lesion around 7 months ago and confirmed that it had grown. Due to the size, growth, and signs of ulceration, the lesion was suspected to be basal cell carcinoma and the patient was referred to an oculoplastic surgeon for further evaluation. At the referral, the lesion was confirmed as a presumed nodular BCC and referred for dermatologic biopsy and coordination for Mohs surgery with oculoplastic repair pending biopsy results for BCC. However, his shaved biopsy revealed a squamous cell carcinoma lesion that was well differentiated and extended to the deep margins of the specimen.

DISCUSSION

DEFINITION AND PATHOPHYSIOLOGY

Basal cell carcinoma arises from basal keratinocytes in the epidermis. Unlike SCC or melanoma, it rarely metastasizes, as it is slow-growing and primarily locally invasive. This lower metastatic potential is largely due to the absence of many molecular drivers that promote aggressive tumor invasion and the development of metastatic cells in squamous cell carcinoma and melanoma such as epithelial-to-mesenchymal transition, angiogenesis and vascular endothelial growth factors.[1] When metastasis does occur, however, it is most often associated with tumors originating in the head and neck, which account for 67 to 85 % of metastatic cases. The disease typically spreads first to the lymph nodes in over 50 % of cases, followed by the lungs in 28 to 33 % and the bones in 20 to 24 %.[1] The morbidity of basal cell carcinoma is primarily because of its ability to erode eyelid structures and infiltrate surrounding tissues if left untreated.[2]

Pathogenesis is linked to mutations in the hedgehog signaling pathway, particularly in the PTCH1 and SMO genes, which result in uncontrolled keratinocyte proliferation and resistance to apoptosis.[2] As the tumor expands, it secretes enzymes that degrade the basement membrane and extracellular matrix, allowing invasion into dermis, muscle, and in advanced cases, orbital tissue. However, orbital invasion is uncommon and reported incidence falls between 1.6 to 2.5%.[2]

Squamous cell carcinoma originates from malignant transformation of squamous keratinocytes, typically demonstrating keratinization and intercellular bridges on histopathology.[3] SCC is more aggressive, with a well-documented capacity to invade local tissues and metastasize to regional lymph nodes.[3] Clinically, SCC often presents with ulceration, crusting, or keratinization, but in early stages it can mimic the nodular or ulcerated appearance of BCC, complicating clinical diagnosis.

In the case presented here, the lesion's nodular appearance and central ulceration suggested a diagnosis of BCC, leading to referral for biopsy and anticipated Mohs micrographic surgery with oculoplastic repair. Pathology, however, revealed a well-differentiated SCC extending to the deep margins of the specimen. This unexpected result emphasizes the limitations of relying on clinical appearance alone, as periocular malignant lesions may mimic one another. It reinforces the principle that histopathology remains the gold standard for establishing a definitive diagnosis and guiding management.

EPIDEMIOLOGY

Basal cell carcinoma accounts for 80 to 90 % of malignant eyelid tumors which makes it the most common periocular malignancy worldwide.[2] Incidence increases with age, and most cases occur between 60 to 80 years old with a slightly higher predominance in males than females.[2] The lower eyelid is affected most frequently as more than 50% of cases affect this region, followed by 30% of cases being the medial canthus, 15% of cases being the upper eyelid, and 5% of cases being the lateral canthus.[2] The theory is that the lower lid may be more affected due to light reflection by the cornea onto the lower lid margin vs the upper lid receiving protection from the eyebrow.[2]

Risk factors include fair complexion, chronic ultraviolet radiation exposure, prior radiation therapy, immunosuppression, and exposure to carcinogens. Genetic conditions such as basal cell nevus syndrome (Gorlin syndrome) also predispose to multiple tumors at younger ages.[2]

Squamous cell carcinoma accounts for 5 to 10% of malignant eyelid tumors.[4] SCC typically presents in a similar demographic as most patients are in their sixth or seventh decade of life.[3-4] with a strong association with chronic sun exposure, fair skin, advancing age, and immunosuppression. Men are two to three times more likely to develop SCC than women.[3]

Additional risk factors include prior radiation exposure, chronic inflammatory eyelid disease such as blepharitis or conjunctivitis, and premalignant lesions including actinic keratosis and Bowen's disease.[4] Unlike BCC, SCC carries a significantly greater risk of metastasis, spreading to regional lymph nodes in up to 24% of cases and to distant sites in 6 to 8% of cases.[3]

SIGNS AND SYMPTOMS

The appearance of BCC varies according to subtype. Nodular BCC, the most common as it accounts for 60 to 80% of cases, presents as a pearly nodule with rolled margins and overlying telangiectatic vessels.[3,5] With time, ulceration may occur, producing the classic "rodent ulcer." Morpheaform BCC accounts for 5 to 10% of cases and appears as a flat, smooth, flesh colored plaque with poorly defined borders and areas of induration.6 It is often more aggressive as it has a higher rate for metastasis, local tissue destruction, a higher rate of incomplete resection, and there is an increased likelihood of local recurrence.[3,5]

Symptoms are often minimal, but patients may report bleeding or crusting. On examination, concerning findings include lash loss, distortion of the eyelid margin, ulceration, or a lesion that fails to heal over weeks to months.

SCC of the eyelid can also vary in appearance depending on the degree of differentiation. Well-differentiated lesions often display keratinization and intercellular bridges, appearing as firm, scaly, or keratinized nodules that may ulcerate or crust.[4] Poorly differentiated lesions tend to grow more aggressively, present with less keratinization, and are more likely to show rapid enlargement and irregular margins.[4]

Clinically, SCC lesions tend to grow faster than BCC and appear more inflamed, with ill-defined borders that can extend into adjacent conjunctiva or skin. Symptoms are often more noticeable with patients' reporting tenderness, recurrent bleeding, or sudden rapid enlargement. Lash loss and eyelid margin distortion are also common in SCC. Perineural invasion, which occurs in 8 to 14 % of facial and periorbital cases, can lead to pain, paresthesia, or issues with ocular motility when cranial nerves are involved.[3]

From a clinical standpoint, the overlapping features such as non-healing ulcer, lash loss, and irregular borders show the necessity for histopathologic confirmation in nearly all suspicious cases.

MANAGEMENT AND TREATMENT

Surgical excision with frozen section margin control is the gold standard treatment.[2] Mohs micrographic surgery is preferred for periocular lesions because it combines the highest cure rates with maximal tissue preservation.[2] Reconstruction may be required to restore eyelid integrity and preserve protection and function of the globe.

Radiation therapy may be considered for patients who are poor surgical candidates, although it is generally less effective in the periocular region and carries risk of ocular complications such as dry eye, cataracts, stenosis of the puncta and ectropion.[2] For advanced or recurrent cases or when surgery is not suitable for BCC, medical therapies such as topical imiquimod or systemic hedgehog pathway inhibitors including vismodegib can be used when surgery or radiation is not feasible.[2] Prognosis is excellent when BCC is diagnosed early and properly excised. Recurrence rates are low, although patients remain at increased risk of developing additional lesions and require long-term monitoring.

Management of SCC is more challenging, and like BCC, surgical excision with margin control is first line. However, high-risk features like poor differentiation, perineural invasion, large tumor size, or invasion into adjacent structures may warrant sentinel lymph node biopsy to evaluate regional involvement. When complete resection

Differentials[6]

Condition	Clinical Features	Clinical Points
Basal Cell Carcinoma	Firm, pearly papule with superficial telangiectasia; Central ulceration and/or necrosis in later stages	Rarely metastatic; localized invasion, commonly presents on the lower lid
Squamous Cell Carcinoma	Scaly, rough, erythematous plaque; ulceration common	Higher metastatic potential; faster growth with keratinization more prominent
Keratoacanthoma	Dome shaped nodule with central keratin filled core	Rapid onset and sometimes spontaneous regression over the course of several months
Chalazion	Firm, painless eyelid lipogranuloma	Often resolves with warm compresses or responds to incision and drainage or steroid injection
Squamous Papilloma	Pedunculated or sessile, smooth lesion	Benign, often multiple; no lash loss
Verruca Vulgaris	Rough, hyperkeratotic lesion associated with human papilloma virus	Viral etiology; often clustered

is not achievable, or margins remain positive despite repeat excision, adjuvant radiation therapy may be indicated.[4] For advanced or metastatic SCC, systemic immunotherapy with immune checkpoint inhibitors is increasingly used. Programmed death-1 (PD-1) inhibitors, such as cemiplimab and pembrolizumab, enhance the immune system's ability to recognize and attack tumor cells and have shown significant efficacy in locally advanced or metastatic SCC.[4]

CONCLUSION

Although basal cell carcinoma is the most common eyelid malignancy, squamous cell carcinoma carries a significantly higher risk of recurrence and metastasis. The case presented here demonstrates how clinical appearance can be misleading and reinforces the principle that biopsy is essential for all suspicious periocular lesions. Proper diagnosis not only guides surgical management but informs the need for systemic evaluation. Recognition of these differences ultimately ensures that patients receive the most appropriate, timely, and potentially life-saving care.

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