

Cutaneous Non-Melanoma Malignancies with Retrobulbar Extension

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Abstract

Cutaneous, non-melanoma malignancies including basal cell and squamous cell carcinoma are fairly slow-growing lesions that, when readily diagnosed and treated early with surgical excision, rarely become problematic. However, if these lesions continue to progress, the potential for invasion of deeper tissues with incomplete excision, as well as locally advanced, recurrent, or metastatic disease, exists. Two cases of cutaneous malignancy, located in the temporal region, with retrobulbar extension are presented: one case of basal cell carcinoma and one case of squamous cell carcinoma. A high index of suspicion is necessary when addressing these locally aggressive, potentially life-threatening lesions.

INTRODUCTION

It is estimated that one million new cases of non-melanoma skin cancer will be diagnosed each year in the United States.¹ The majority of these lesions occur in the head and neck region, and are treated by Mohs micrographic surgery, cryosurgery, shave biopsy and electrocauterization, radiotherapy, and/or local surgical excision. Basal cell carcinoma (BCC) is the most common malignant periorbital tumor and accounts for 90 percent of eyelid malignancies.² Squamous cell carcinoma (SCC), also frequently diagnosed in the periorbital area, may have a more aggressive course and higher metastatic potential than basal cell carcinoma, but still may be adequately treated surgically before local invasion or tumor spread occurs.

Although most of these cases can be treated adequately with surgical excision, these lesions have the potential to cause extensive local tissue destruction, metastasize to other regions, and even cause death. In advanced cases, the clinically visible tumor surface may only represent one-fifth of its microscopic invasion: as visual indicators of tumor spread often underestimate the full extent of the lesion, incomplete excision significantly increases the likelihood of recurrence.¹ The periorbital area poses a particular challenge, due to its concentration of important structures such as the upper and lower eyelid with their appendages, the lacrimal gland, the nasolacrimal gland, and the globe itself. Although locally invasive disease from cutaneous basal cell and squamous cell carcinoma does not usually develop, the

possibility of orbital and intracranial invasion must be carefully considered, given the potential for perineural invasion or the spread of tumor along the periosteum of the medial and possibly lateral orbital walls, first described by Mohs in 1955.^{2,3,4} Consequently, it is crucial to identify lesions that are at high risk of subclinical spread in order to appropriately address the primary tumor and minimize the risk of local recurrence and invasive disease. The following cases describe two patients with periorbital cutaneous malignancy with retrobulbar extension. Although both patients were being closely followed by several disciplines including plastic surgery, ophthalmology, and otolaryngology, the combination of local recurrence, tumor aggressiveness, and subclinical presentation illustrate the insidious nature of locally invasive disease and the challenges in further management of these patients.

CASE REPORTS

CASE 1

A 65 year old white male with an extensive history of basal cell and squamous cell carcinomas of the face presented with several suspicious appearing lesions, one of which involved his left cheek/temple area. Prior to our consultation, the patient had undergone external beam radiation to the periorbital areas for previous skin cancer treatment. Surgical excision was undertaken. Histology confirmed basal cell carcinoma, with morpheaform components and surgical margins were free of tumor. The patient returned for follow-up after initial complete healing, and had developed other

skin lesions, one of which again involved the areas of the left cheek/temple. Surgical excision was again undertaken, and histology indicated recurrent disease with perineural invasion at the deep margin; but indicated clearance of tumor margins. He subsequently underwent four additional procedures within the ensuing five years to address various new facial skin lesions, all basal cell carcinomas, one of which appeared to be re-recurrence at the left cheek/temple region.

Recommendation for radical resection / reconstruction of the left cheek/temple lesion area the left cheek/temple lesion/region was discussed with the patient, however he refused in favor of additional radiation therapy to the region. His disease was un-responsive progressed, with onset of left facial nerve palsy and proptosis, conjunctival edema, and restriction of extraocular eye movements. An MRI demonstrated a mass involving the lateral left orbit, extending to the cavernous sinus. Rapidly progressing exposure keratitis of the left eye ensued. Image-guided biopsy confirmed basal cell carcinoma. His course rapidly progressed despite continued radiation therapy, and the patient soon expired.

CASE 2

A 74 year old white male with an extensive history of skin cancer including basal cell and squamous cell carcinoma of the face presented with multiple suspicious lesions involving his right cheek and right lateral canthal/temporal region. At the time of surgical excision of his right lateral canthal lesion, a canthoplasty was incorporated into the reconstruction and to correct ectropion of his right lower eyelid. The right cheek lesion was excised and reconstructed. Histology confirmed squamous cell carcinoma with negative surgical margins at both sites.

Excision of a new suspicious lesion involving the right temple area was performed one year later, again histology confirmed squamous cell carcinoma. The patient began to exhibit visual symptoms including diplopia approximately 2 years later. CT scan demonstrated a large mass within the posterior orbit with bony erosion and destruction of the posterolateral orbital wall. Radiographically, the tumor extended from scar to invade the deeper structures. The patient's symptoms rapidly progressed to a frozen globe and total blindness in the right eye. Radiographically the tumor extended from the right cheek scar to invade the deeper structures. Biopsy of the tumor confirmed invasive squamous cell carcinoma. Orbital exenteration was

recommended; however, the patient declined surgical intervention, and he was initiated on chemotherapy with concomitant radiation therapy.

DISCUSSION

Orbital invasion from cutaneous basal cell and squamous cell carcinoma is a rare occurrence: multiple studies have demonstrated an incidence less than 5 percent (range, 0.8 – 3.8 percent) for basal cell carcinoma,² and between 0.2 percent up to 8.2 percent in the case of squamous cell carcinoma.³ In spite of the relative infrequency of invasive disease, massive facial lesions still can result, due to a combination of patient delay and tumor aggressiveness.⁶ These lesions have a propensity for local invasion and recurrence, often attributed to conservative, occasionally inadequate, initial therapy aimed at preserving critical periorbital structures.^{6,7} This is especially true for lesions of the medial canthus, with its extensive network of blood vessels and nerves extending posteriorly into the orbit and the nasolacrimal drainage system. Most patients being considered for orbital exenteration to manage invasive disease have already failed previous attempts at more conservative surgical excision or radiation therapy.⁶ As the incidence of recurrent disease after exenteration can be as high as 50-75 percent, the importance of appropriate, early management of these lesions on initial presentation cannot be overemphasized.^{8,9}

Basal cell carcinoma is most commonly diagnosed in patients between 40 and 80 years of age, with a slight male preponderance.² In comparison, several studies have demonstrated the average age at diagnosis of orbital invasion to be during the seventh decade, with a much higher incidence in males: Leibovitch et al describe an average age of 70 with a male to female ratio of 3:1 for invasive basal cell carcinoma, while Howard et al documented an average age of 75.8 years and a similar male to female ratio in a review of cases of invasive basal cell and squamous cell carcinoma.^{2,5} This consistent male preponderance for orbital invasion suggests that men are at greater risk than women, possibly due to more aggressive tumors, potential delay in diagnosis, or delay in seeking treatment.

The clinical presentation of invasive periorbital lesions can be fairly subtle and are frequently asymptomatic. Patients typically present with an indurated, palpable, or ulcerated mass, which is often times painless. In Leibovitch et al's review, 35.7 percent of these lesions were fixed to bone.² Limited ocular motility, due to involvement of the

extraocular muscles, is another common finding, with an incidence between 30.4 percent up to 76.9 percent.^{2,5} Globe displacement, a worrisome finding, was present in 17.8 percent.² Although most patients present with symptoms of a mass often accompanied by diplopia, up to 35.7 percent of patients had only a visible or palpable mass, with no bone fixation or orbital signs. Even with obvious clinical signs of epiphora or exposure keratopathy, symptomatic complaints were not usually volunteered by patients.⁵ These findings were noted in both of the cases presented, both patients had recurrent episodes of conjunctivitis from exposure keratitis, likely secondary to proptosis from retrobulbar extension of tumor. Strabismus was a late finding in both cases, and was accompanied by cranial nerve involvement and bony invasion. Orbital invasion may often be entirely asymptomatic, without orbital signs or visual disturbances until late in the course of the disease: the diagnosis requires a high index of suspicion to allow for early therapeutic intervention.²

Long-standing or neglected tumors, as well as recurrent or incompletely excised tumors, are considered to be contributing factors to more aggressive, invasive lesions. Orbital invasion from basal cell carcinoma may develop over period of seven to ten years from the initial diagnosis.^{2,5} Direct orbital invasion from squamous cell carcinoma, in comparison, develops much more rapidly than disease resulting from basal cell lesions. No difference in disease progression has been identified between patients who underwent repeated excision and those who did not seek any previous medical treatment of cutaneous lesions. Most patients (84.4 percent) with invasive cutaneous non-melanoma lesions had a previous history of recurrent or incompletely excised tumor, though many may be due to late or delayed presentation.^{2,5}

Tumor location has been mentioned as a possible risk factor for potential invasion: lesions of the medial canthus may rapidly involve the nasal bones or penetrate the thin medial orbital wall to involve the ethmoid sinus, while upper lid and supraorbital lesions commonly invade the frontal bone, subsequently eroding into the dura and frontal lobe. The lower lid is the most common site of initial presentation of periorbital basal cell carcinoma, accounting for approximately 47 percent of lesions.² The medial canthus is also a common location, ranging from 28 - 56 percent of periocular tumors. Several studies have emphasized an association between medial canthal basal cell carcinoma and an increased risk of orbital invasion and death.² Mohs, in

1955, noted that many recurrent medial canthal tumors extend deeply along the periosteum of the medial orbital wall. He postulated that sheets of tumor have the propensity to spread along the orbital walls.⁴ The close proximity of the skin to the periosteum in the medial and lateral canthal areas also may predispose to orbital involvement in these sites. Medial canthal tumors comprised approximately 56 percent of invasive lesions, while lateral canthal lesions contributed an additional 18 percent.^{2,5} There is no clear indication that the treatment of medial canthal lesions or delay in diagnosis of orbital invasion differed from those in the lateral canthal region.⁵ Also, there does not appear to be a correlation between medial canthal tumor location, invasion, and death, although the small number of patients in this study may have been a limiting factor.⁵

Tumor histology and subtype has clearly been demonstrated to be a prognostic factor for invasiveness and malignant potential. In the case of basal cell carcinoma, the different histologic subtypes have differing degrees of aggressiveness. The nodular and superficial subtypes tend to be less aggressive, while the morpheaform, infiltrating, and basosquamous subtypes tend to be more invasive, with a higher incidence of subclinical invasion, a higher rate of residual positive margins after excision, and a greater risk of recurrence and metastasis. The morphea subtype is especially infiltrative, and has the capacity to invade deeply into orbital tissues. In addition, recurrent basal cell carcinoma on histology is often a mixture of scar tissue and basaloid cells, making pathologic identification of margins difficult on repeat excision. While the more aggressive infiltrative or morpheaform/sclerosing subtypes are reported to make up only five to seven percent of all skin basal cell carcinomas, these histologic subtypes comprise more than 80 percent of invasive periorbital lesions.^{2,5}

Richmond and Davie postulate that incomplete excision may contribute to the evolution of invasive basal cell carcinoma, as the presence of scar tissue may obscure monitoring and delays clinical detection of recurrence.¹⁰ Also, fibrosis from previous inadequate excision or radiotherapy may entrap malignant cells and prevent upward migration to the skin surface, favoring deep, subclinical extension into surrounding tissues. Tumors with more aggressive histologic subtypes may be more likely to be incompletely excised: a majority of patients reported with aggressive subtypes of cutaneous malignancy had positive margins following initial tumor excision. Complete histologic clearance in the context of potentially invasive disease should be emphasized,

especially in this patient population.^{2,5,10}

Perineural invasion, in which tumor cells spread in and around adjacent nerves, is an uncommon finding in cutaneous malignancies; tumors exhibiting perineural invasion are more aggressive and demonstrate higher rates of recurrence, morbidity, and mortality. It is believed that the low resistance cleavage plane of the perineural sheath may allow rapid and broad tumor extension. Perineural invasion has been reported to occur in 2.4 percent up to 14 percent of patients with squamous cell carcinoma; basal cell carcinoma can spread through this route as well. The tendency of these tumors to infiltrate along nerves is also an ominous finding, suggesting probable invasion into the orbit and skull along the cranial nerves. Several reports indicate findings such as isolated or multiple cranial neuropathies, pain, anesthesia, or paresthesia, facial paralysis, diplopia, and trismus as potential signs of perineural invasion. However, up to 60 percent of patients may be asymptomatic in the early stages of their disease.^{2,3,5}

Perineural invasion may also be suspected when enlargement or enhancement of the cranial nerves is noted radiographically. Histologic evidence of perineural invasion on biopsy specimens also will confirm the diagnosis, as demonstrated in Case #1. In the case of basal cell carcinoma, perineural invasion may be a late finding, long after primary tumor resection, and there may be skip areas that complicate margin assessment. Imaging studies may also yield falsely negative results in up to 45 percent of patients with this condition, consequently, a high level of suspicion is necessary for early diagnosis and the initiation of appropriate treatment.^{2,3}

Batra and Kelley developed a risk scale for predicting extensive subclinical spread of basal cell and squamous cell carcinoma, based on a multivariate analysis of 1095 cases.¹ Variables including age, gender, immune status, anatomic location, and histologic subtype were assessed in combination. Significant predictors included: basosquamous, morpheaform, nodular, and recurrent BCC subtypes located on the nose; morpheaform BCC on the cheek, either tumor type on the eyelid, temple, or ear helix; either tumor type on the neck in men; recurrent BCC in men; and preoperative size 10mm or greater.¹ As patient-specific and tumor-specific characteristics are included simultaneously, this provides a more thorough assessment of the probability of subclinical spread associated with these combinations of risk factors.

Aggressive therapy is recommended for patients with early indications of locally invasive disease. This typically involves early adequate resection of involved tissues, appropriate regional lymphadenectomy, if indicated, and postoperative radiotherapy. In cases of documented orbital invasion, treatment typically consists of exenteration with or without subsequent radiotherapy, although a smaller percentage of patients have been treated more conservatively with local excision or radiotherapy alone, or with a combination of both modalities.^{2,6,8,10} Surgical resection with clear excision margins may prevent local recurrence, but this does not address the possibility of micrometastatic disease to regional lymph nodes or distant organs; consequently, orbital exenteration should not be considered a curative procedure in most cases without adjunctive therapy.¹¹ In both of the presented cases, the recurrence of disease following multiple adequate excisions is clearly worrisome for aggressive, potentially invasive disease. Mohs micrographic surgery may play an important role in critical locations such as the periorbital area.

Regional metastasis have also been associated with tumors exhibiting high pathological grade such as moderately and poorly differentiated squamous cell carcinoma and relatively large (four centimeters or larger) primary tumors.¹² With periorbital lesions, careful assessment of both the submandibular and parotid region lymph nodes, as well as potential spread to subsequent level II cervical lymph nodes is important. Despite an absence of regional metastasis on initial presentation, prophylactic management of the parotid lymph nodal group may be indicated in cases with a high risk of metastasis.¹² Postoperative radiotherapy has frequently been utilized in cases with indistinct margins, for aggressive tumor subtypes, or in cases of perineural invasion.^{2,5,9} In the instance of extensive unresectable disease, external beam radiation may be offered to patients. Although long-term cure may not be achieved, radiation therapy may prolong the disease-free interval. In equivocal cases, a supraorbital nerve biopsy may confirm the diagnosis in patients with evidence of local recurrence or suspected perineural invasion.³

CONCLUSIONS

Orbital invasion from basal cell and squamous cell carcinoma is an infrequent occurrence, accounting for less than ten percent of all nonmelanomatous skin cancers. Although the incidence is rare, the complications and outcomes associated with invasive disease warrant early diagnosis and treatment. Adequate excision of suspicious lesions, histologic confirmation of negative margins,

recurrent disease, canthal tumors, aggressive histologic subtypes, and lesions with clinical or histologic signs of perineural invasion., all require an aggressive approach. Once orbital invasion is confirmed, appropriate management including excision or orbital exenteration, assessment of regional lymph node status, and postoperative radiotherapy should be considered.

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