Keratoacanthoma vs. Squamous Cell Carcinoma of the Eyelid: Case Report, Histopathological Update and Treatment Modalities

Abstract

Keratoacanthoma (KA) and Squamous Cell Carcinoma (SCC) are entities that often have been difficult to differentiate. Current thought establishes that Keratoacanthoma behaves similarly to a low-grade squamous cell carcinoma. We present a case of an 80 year old female which history of present illness as well as clinical impression mimics Keratoacanthoma (KA), but on histopathological examination resulted in Squamous Cell Carcinoma (SCC). We posit the use of novel histopathological and cytological advances, such as TGF-β sequencing and TGF-Alpha staining in assessing the specimen. Subtle differences should guide treatment for patients that need further resection and that might have orbital involvement.

Introduction

Keratoacanthoma and Squamous Cell Carcinomas of the eyelid have been thoroughly discussed in conjunction as arising from similar cellular origins. The length of time in which the lesion develops might be key since both lesion tend to overlap in their clinical appearance. Both tend to present as hyperkeratotic lesions with cellular debris with an ulcerated and a well circumscribed base. Keratoacanthomas tend to develop rapidly, while squamous cells carcinomas have a more insidious course.

Histologically Keratoacanthomas form a crater in the center of the lesion and tumor cells have a glassy cytoplasm. Furthermore, the expanding edge of the Keratoacanthoma engulfs elastic fibers. None of these features are characteristic for ordinary Squamous Cell Carcinoma which presents with abundant eosinophilic cytoplasm and a large, often vesicular nucleus. Inflammation around vessels and nerve sheaths is common in Squamous Cell Carcinomas infiltrative lesions.

New staining and cytochemical methods of analysis should be explored in patients where the prognosis is equivocal. Further resection of the tumor and closure of the surgical wound should be delayed in cases were there is no conclusive histopathology.

Case Reports

An 80 year old female with a past medical history of hypertension, non-insulin dependent diabetes, tobacco abuse and dementia is referred to the department of Ophthalmology due to an unsightly lesion on the right medial canthus. The patient is accompanied by her daughter. Patient’s daughter states that lesion has been slowly getting larger in size over the period of 2 months. Patient complains of itching on eyelids, as well.

Patient presents with best corrected visual acuity of counting fingers at 2 feet, in both eyes. A 3cm by 4cm lesion, well circumscribed, with sharp borders is seen and measured on the right medial canthus. The lesion extends to the nasal bridge. The lesion’s central zone seemed at moment of presentation to be eroding and exhibiting excessive epithelial debris. Another 0.5mm by 0.4mm yellowish wax-like lesion was noted in the left upper eyelid area. Bilateral infraorbital erythema was noted. Lesion was mildly tender to touch. Severe blepharitis and Meibomian gland inspissation was present bilaterally. Patient presents with mild conjunctival hyperemia. Superficial punctate keratitis was present in both eyes. Patient presented Nuclear Sclerotic Cataracts +3. Fundus examination was difficult given the patient’s mature cataracts.

With a suspicion for malignancy a wide edge recession of the mass was advised. The patient was taken to the operating room. Careful dissection was initiated. It was found that the lesion had eroded down to the periosteum, and nasal bone had to be resected. The canalicular system was inspected. No damage was found. Specimen was sent to pathology. Lesion was dressed and antibiotic ointment placed...
over lesion edges. Lesion was not closed until specimen was evaluated by histopathologist.

Subsequently, specimen was reviewed by histopathologist revealing Squamous Cell Carcinoma with perineurial invasion, with further involvement of the nasal and deep edges.

**Discussion**

Keratoacanthoma is a benign epithelial neoplasm first described by Dr. Jonathan Hutchinson in 1889 as a “crateriform ulcer of the face”. It usually presents as a solitary rapidly growing lesion and is associated with sun-exposed skin. Squamous Cell carcinomas tend to be flat flaky lesion with a red base, which tend to occur at the lower eyelid. Their etiology is diverse, with some shared commonalities. Causes of these tumors mainly include ultraviolet exposure and radiation. KA was thought at one point to be related to human papilloma virus (HPV) infection. A study by Forsulund, et al. Describes that by the use of PCR, cutaneous HPV DNA was detected in 51% (37/72) of the KAs2. On the other hand, HPV has not been found to actually be part of the tumorigenesis of SCC3.

Other causes of Keratoacanthoma include immunosuppression, including diabetes and renal dialysis4. These systemic conditions have not been related to an increased incidence of SCC.

Differences in the past medical history are important when evaluating the presentation of the patient. Particular details about the patient’s history might aid in assessing the specific profile of the lesion in question.

In instances where multiple lesions are found in the young, genetic causes should be considered. Multiple Self-Healing Squamous Epitheliommas (Ferguson-Smith Disease), or Muir-Torre syndrome. The latter has been associated with loss of TGFβRI function. The genetic relationship of KA and SCC has been recently explored. A recent study by Goudie et al. Posits that SCC and KA share the same loss of function of TGF-β transducing signals.

In another study by Cabrijan et al. In order to further investigate and to assess the possible differences in transforming growth factor-alpha (TGF-alpha) expression between SCC and KA, 40 skin tumor specimens were studied. 20 cases of each SCC and KA were analyzed immunohystochemically. There were significant differences established in staining patterns between KA and SCC. In the case of KA the study detected TGF-alpha staining diffusely (90% of cases) and without peripheral staining of cells in 1-2 layers (60% of cases). While for SCCs there was patchy staining (55% of cases) with peripheral staining of cells in 1-2 layers (100% of cases). These histological differences might help in differentiating the tumors, while helping to devise a sound surgical plan6.

Regarding the invasive behavior of SCC a study conducted by Soysal et al. With a sample size of 76 patients established that the recurrence rate or presence of residual tumor was approximately 22.4% and most of them actually had some degree of orbital involvement. Regional lymph node metastasis was detected in 5 (6.6%) cases. Advanced deep local invasion was not rare in their study likely caused by treatment delay and previous inadequate treatments such as complete resection of the tumor. Adverse prognostic factors associated with secondary orbital invasion are previous recurrences, extended duration of lesion, larger lesion size, and presence of perineural invasion on histopathological analysis.8

The treatment of precancerous lesions is paramount to avoid development of SCC8. Once the diagnosis of SCC has been established the prognosis and survival rate change drastically. Even though SCC is the second most common eyelid tumor, after basal cell carcinoma, its course is more rapid and much more aggressive. Periocular SCC can metastasize and invade the orbital and intracranial space, thus increasing its mortality and morbidity exponentially.9 Since there are no pathognomonic features that
make it easy to differentiate SCC from lesions such as KA, it is recommended that all KAs be managed as SCCs until a definitive diagnosis is established.

The behavior of SCCs range widely in aggression and therefore its management should be individualized based on the presenting features of the tumor (size, location, subtype, recurrence, perineural invasion) and patient factors (age, health)1. SCC particularly in the periorcular region is considered to be a high-risk area with a high metastatic rate because of its tendency towards perineural invasion (PNI), being the periorcular area a vastly innervated anatomical landmark. PNI occurs only in 5% of SCC, but once it occurs most patients had a substantial decrease in their five year life expectancy3, due to its proclivity to extend intracranially.

There are several methods of treatment for these tumors. Surgical resection has been the mainstay of treatment for KA as well as SCC. In the case of SCC surgical resection might be followed by adjuvants such as cryotherapy, chemotherapy, and radiation therapy in situations that the lesion proves difficult to resect. Mohs’s micrographic surgery has been proven to be the most successful surgical approach given its careful management of tissue and margin control in a high-risk area such as the eyelid. Moh’s micrographic surgery provides better tissue conservation for acceptable cosmetic results12,13. When dealing with tumors of the periorcular area excision and curettage should not be considered as a primary treatment option because it does not allow for histopathological testing. Excision and curettage tend to leave thicker scars which prevents prompt diagnosis of cancer recurrence (common in SCC), and it does not permit the desired cosmetic result13. Cryotherapy can be used in patients with bleeding disorders or other contraindications for surgery. This approach does not allow margin control and lesions tend to recur after 2 years14. In high-risk areas, 6mm margins are recommended15 with a 95% chance of total resection16. The tumor depth and extent may be difficult to define since SCC frequently presents with associated inflammation and surrounding precancerous lesions17. These margin recommendations should be taken only as a guideline, since large and aggressive lesions frequently have extension beyond the apparent superficial boundary.

Radiotherapy as a primary treatment is usually considered when a patient cannot undergo a surgical excision or as an adjuvant in cases where there is perineural invasion or regional metastasis. The decision of using this modality of treatment depends on the clinician’s judgment since there has not been comparative studies of surgery vs surgery/radiotherapy for high risk SCC18,19.

Chemotherapy can be used as an adjuvant in select high risk cases of SCC or in metastatic cases. Topical chemotherapeutic agents such as 5-fluorouracil or imiquimod are not preferred in the periorcular area because of their tend to cause considerable ocular irritation. The most common drugs are cisplatin and carboplatin, being nontarget drugs. Lately there has been increasing evidence of the use of cetuximab, a chimeric immunoglobulin GI monoclonal antibody that inhibits the epidermal growth factor receptor targeting specific cells in the SCC society20,21.

Regarding our patient, we informed her and her daughter of the limited treatment modalities given the degree of the lesion and its depth. Patient was referred to radiation oncology for evaluation of the lesion and proton beam therapy. Given the depth of the lesion exenteration might be considered depending on the success or failure of future radiotherapy.