Eastern Ophthalmic Pathology Society Meeting

Washington, DC

September 13-15th, 2018

Nora V. Laver, MD

Director, Ocular Pathology Lab

Associate Professor of Ophthalmology and Pathology

New England Eye Center and Tufts Medical Center; Tufts University School of Medicine

800 Washington Street, #6700, Boston, MA 02111

Tel: 617-636-1035; cell 617-909-9076

Email: nlaver@tuftsmedicalcenter.org; laver.nora@gmail.com

Distributed: protocol and a glass slide

Conjunctival Mass in Atopic Dermatitis

Introduction

Atopic blepharitis is one of the major ocular complications of atopic dermatitis. Atopic dermatitis is a common skin disease associated with other allergic diatheses. Ocular complications have been reported in up to 42.5% patients and include blepharoconjunctivitis, cataracts, corneal disease and ocular herpes simplex infection. Atopic dermatitis is recognized as a predisposing factor for development of cutaneous squamous cell carcinoma. The present case is an unusual case of metastatic conjunctival squamous cell carcinoma in a patient with long standing atopic dermatitis.

Case Presentation

A 64-year-old male presented to the New England Eye Center Cornea clinic on for evaluation of a lesion on his left lower eye lid that he first noticed two months earlier. Since first noticing the growth, the lesion had steadily enlarged causing a foreign body sensation and light sensitivity that ultimately prompted him to seek attention from an ophthalmologist.

The patient had a long history of bilateral severe ocular atopic dermatitis, rosacea, multiple environmental allergies and asthma, as well as cardiovascular disease (HTN, HLD, DM). He was a retired military officer, former smoker (1.5 ppd x 40 years), and had a prior history of alcohol abuse. His medications included PredForte drops, Protopic ointment OU, Ventolin HFA, Diovan and Qvar.

On examination, his VA was 20/70 OD and 20/100 OS. Extra ocular movements were restricted in all directions in the left eye. The eyelids were noted to be edematous with thick, keratinized lid margins, complete madarosis, and cicatricial extropion OU. His conjunctiva was diffusely injected with foreshortened fornices OU. OS had a 5 mm papillomatous sessile mass on the temporal conjunctiva with extension onto the cornea between 2 to 5 o'clock. The corneas had dense anterior neovascularization with stromal haze 360 degrees OU, which was his baseline secondary atopic disease. Anterior chamber

and dilated fundus exam were within normal limits. External exam was additionally notable for a palpable pre-auricular lymph node

The patient had a diagnostic incisional biopsy. Histopathology showed an invasive, papillary well to moderately differentiated squamous cell carcinoma of the conjunctiva. The tumor extended to the edges of the biopsy and showed features of HPV infection.

A CT of the head was obtained, revealing a 2.3 cm left lateral conjunctival mass abutting the lacrimal gland and a 2.5 cm left parotid mass. The patient subsequently underwent excision of the conjunctival mass by Ophthalmology and a parotidectomy with radical neck dissection by ENT, and application of 5-FU. Histopathology revealed tumor present at the margins with suspected lymphovascular invasion of the conjunctiva. 1 out of 21 cervical lymph nodes was positive for metastatic squamous cell carcinoma. Due to the positive margins, the patient opted for exenteration followed by radiation to the orbit, parotid and neck. Two months later a second suspicious lesion was excised from the right upper eyelid also revealing squamous cell carcinoma. The patient did well for 6 months, but then presented with new neck masses. Repeat radical neck dissection was performed, with pathology this time showing a poorly differentiated SCC. Subsequent follow up imaging revealed new enlarged hilar lymph nodes with bony metastasis, and a mass encasing the carotid. The patient expired one year after initial presentation.

Discussion

This is an unusual case of conjunctival squamous cell carcinoma (CSCC) with widespread metastasis. While CSCC is the most common ocular malignancy, it is still itself a rare entity with an incidence of 8.4 per 10^6. Risk factors include UV exposure, immune compromise, HPV infection, and smoking, and it is further associated with male sex and older age. When confronted with a new conjunctival lesion, the ophthalmologist's initial management options include observation with frequent examinations every 6 months and careful documentation of tumor with slit lamp photos, or biopsy if there is higher concern for malignancy. Observation is reasonable for lesions that do not have concerning features such as marked elevation, extensive pigmentation, fixation to underlying tissues, prominent feeder vessels or palpable lymph nodes. If a decision is made to biopsy, excisional biopsy is preferred to avoid microscopic seeding of tumor cells, however, if the tumor is large (>4mm) and pathology is needed to help guide initial therapy, as in the case presented here, incisional biopsy can reasonably be performed.

The differential diagnosis includes epithelial tumors (squamous papilloma, CIN, SCC, mucoepidermoid and spindle cell carcinoma), glandular tumors (oncocytoma , sebaceous carcinoma), neuroectodermal tumors (melanoma, leiomyosarcoma), neurogenic tumors (neuroma, neurofibroma), and vascular (hemangioma, pyogenic granuloma, Kaposi's sarcoma, lymphatic). Conjunctival tumors can also represent metastasis tumors.

Most CSCC tumors are treated with adjuvant cryotherapy at the time of excision to target any microscopic clusters of tumor cells left behind during surgery. Larger lesions with more aggressive behavior or pathologic features require adjuvant chemotherapy with topical interferon, mitomycin or 5FU after surgery. Diffuse, incompletely excised lesions, or lesions that have recurred multiple times may require radiation. Recurrence of CSCC has an incidence in published literature that ranges widely

from 5.3 – 27% and is associated with size >5 mm and increased depth of local invasion at presentation. Tumors presenting with these features should be treated more aggressively upfront to prevent ocular morbidity or even mortality.

At its worst, CSCC is most often a locally destructive, vision-threatening disease with ocular and orbital invasion rates of 11-13% and 2-15% respectively. Metastatic disease is very rare with few cases reported in the literature. There have been several small case series over the past 40 years that have reported an incidence of metastasis ranging from 1-8%. One such series by Johnson et al. looked specifically at 30 cases of CSCC presenting with orbital invasion, and among this patient population, 23% developed distant metastasis and 100% of those patients ultimately died after aggressive upfront treatment with exenteration and radiation. Clearly, metastatic CSCC is a deadly disease, and invasion into the globe or orbit at the time of presentation is a strong predictor of poor outcome. As in our case, the most common sites of metastasis reported in the literature include the parotid gland, submandibular and submaxillary glands, preauricular and cervical lymph nodes, lung and bone.

Given the often-deadly ramifications of metastatic disease, further features that could help risk stratify patients at initial presentation would be highly valuable to the evaluating clinician. The population studied in the Johnson et al paper experienced an unusually high incidence of aggressive and deadly CSCC, and as a result he and his colleagues were able to identify other features unique to their population that may be associated with invasive disease. For instance, 10 % of the patients in the study had a second primary tumor at presentation, suggesting a possible genetic predisposition. This is similar to the rate described among patients with invasive disease in another study by Iliff et al (7%). Both Johnson and Iliff found that a delay in presentation to medical personnel of 6 months or more is a very strong predictor of invasive disease, suggesting that any case of CSCC has the potential to be deadly if not dealt with in a timely fashion. Lastly, the population studied in the Johnson paper had a high endemic rate of chronic ocular infections, such as trachoma, suggesting that chronic inflammation may play a role.

Interestingly, the patient presented with CSCC arising from an area of long standing inflammation, specifically chronic, severe, atopic dermatitis. In fact, the patient ultimately developed two separate SCC lesions in both eyes. Atopic dermatitis is recognized as a predisposing factor for development of cutaneous SCC. Several large-scale epidemiologic studies have shown an increased incidence of cutaneous SCC among patients with atopic dermatitis compared to the general the population (OR 1.5 – 2.5). Various mechanisms have been proposed for this predisposition including high rates of immune-modulating medications among atopic patients. Glucocorticoids in particular have been showed to increase the risk of non-melanoma skin cancers. T cell dysregulation may also play a role; atopic eczema had been shown to involve a disturbance of T cell maturation, and it is known that SCC has a high incidence among patients with HIV, a disease which causes down-regulation of T cells. Elevated IgE levels are a marker for allergic and atopic disease, and high IgE levels have been shown to correlate with an elevated risk of SCC, possibly due to interference with mononuclear cells' tumor killing capacity. Lastly, inflammatory mediators such as metalloproteinases and oxygen free radicals have been shown to be mutogenic to lung tissue in asthma, another atopic disease.

Conclusion

Metastatic CSCC is a rare but deadly disease, and when evaluating conjunctival lesions, the clinician must maintain a high index of suspicion particularly among patients with delayed presentation, a history of chronic inflammation, or a history of multiple cancers, as definitive action in early invasive disease may ultimately mean the difference between life and death

Selected References

McKelvie, Daniell M, McNab A, Loughnan M, Santamaria JD. Squamous cell carcinoma of the conjunctiva: a series of 26 cases. Br J Ophthalmol 2002; 86:168–173.

Bhattacharyya, N, Wenokur RK, Rubin PAD, Metastasis of Squamous Cell Carcinoma of the Conjunctiva: Case Report and Review of the Literature, American Journal of Otolaryngology 1997; 18 (3):217-219.

Iliff WJ, Marback R, Green WR. Invasive Squamous Cell Carcinoma of the Conjunctiva. Arch Ophthalmol 1975; 93 (2): 119-122.

Jensen AO, et al. Atopic Dermatitis and Risk of Skin Cancer A Danish Nationwide Cohort Study (1977–2006). Am J Clin Dermatol 2012; 13 (1): 29-36.

Cho JD, David DMR, Wetter DA, Bartley AC, Brewer JD. Association between atopic dermatitis and squamous cell carcinoma: a case-control study. International J Dermatol 2017; 57(3): 313-316.

Kao AA. Clinicopathologic Correlation of Ocular Surface Squamous Neoplasms at Bascom Palmer Eye Institute: 2001 to 2010. Ophthalmology 2012; 119:1773–1776.

Rundle P, Mudhar HS, Rennie I. Conjunctival intra-epithelial neoplasia occurring in young patients with asthma. Eye 2010; 24, 1182–1185

Cheng J, et al. History of Allergy and Atopic Dermatitis in Relation to Squamous Cell and Basal Cell Carcinoma of the Skin Cancer. Epidemiol Biomarkers Prev. 2015; 24(4): 749–754.

Flynn TH, et al. Ocular surface squamous neoplasia in an immunosuppressed patient with atopic Keratoconjunctivitis. Int Ophthalmol 2012; 32:471–473.

Galor A, Karp CL, Oellers P, Kao AA, Abdelaziz A, Feuer W, Dubovy SR. Predictors of Ocular Surface Squamous Neoplasia Recurrence after Excisional Surgery, Ophthalmology 2012; 119 (10): 1974-1981.

Ramberg I, et al. Squamous cell dysplasia and carcinoma of the conjunctiva. A nationwide, retrospective, epidemiological study of Danish patients. Acta Ophthalmol. 2015; 93: 663–666

Johnson TE, Tabbara KF, Weatherhead RG, et al. Secondary Squamous Cell Carcinoma of the Orbit, Arch Ophthalm 1997; 115:77-78.

Yousef YA, Finger PT. Squamous Carcinoma and Dysplasia of the Conjunctiva and Cornea: An Analysis of 101 Cases. Ophthalmology 2012; 119 (2):233-240.

Heinz C, et al. Squamous Cell Carcinoma of the Conjunctiva in Patients with Atopic Eczema. Cornea 2003; 22(2): 135–137.

Shields CL, SHields JA. Tumors of the Conjunctiva and Cornea. Survey of Ophthalmology 2004; 49 (1): 3-24.

Shields JA, Shields CL, Gunduz K, *et al.* Intraocular invasion of conjunctival squamous cell carcinoma in five patients. The 1998 Pan American Lecture. Ophthal Plastic Reconstruct Surg 1999; 15:153–160.