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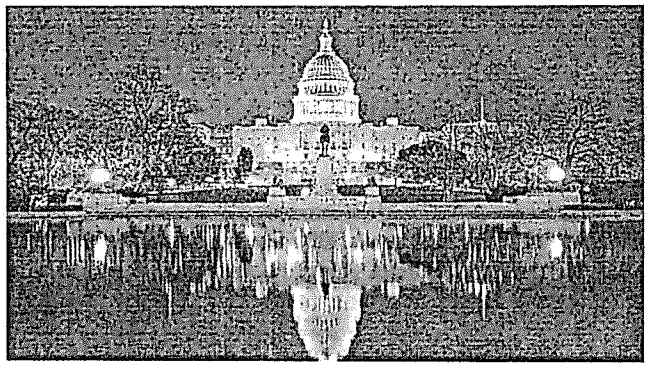

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Mystery Case: Highly aggressive conjunctival tumor

Case Presentation

An 83-year-old Caucasian male was noted to have hyperkeratosis on the surface of the right eye in June 2017. The lesion showed progression and he was referred to the Oncology Service in November, 2017. The pseudophakic right eye had 20/60 vision and the left eye had 20/30.

On examination, the right eye demonstrated an elevated yellow-white mass temporal to the corneoscleral limbus measuring 10 x 10 mm in base and 3 mm in thickness. There were large feeder blood vessels surrounding the lesion. The surface of the mass was dry with leukoplakia and corneal extension was documented. Ultrasound biomicroscopy revealed that the underlying sclera was intact. Ophthalmoscopy of both eyes revealed normal fundus findings.

These features were consistent with conjunctival squamous cell carcinoma. We elected to surgically remove the lesion intact followed by additional freeze-thaw cryotherapy around the margins. At the time of surgery, the mass was friable but we believed that all visible tumor was removed. Conjunctival reconstruction was achieved with sliding flaps.

Microscopic Description

The sections demonstrated a segment of bulbar and limbal conjunctiva. The adjacent conjunctival epithelium demonstrated an abrupt transition into an acanthotic, dysplastic, and markedly parakeratotic epithelium. Surprisingly, nests of atypical, keratinizing squamous epithelial cells were present in the underlying stroma, including the deep surgical margin of resection and in the separately submitted fibrous lateral rectus muscle insertion. There was no lymphovascular or perineural invasion. The peripheral margins were free of carcinoma.

The final diagnosis was invasive squamous cell carcinoma (well to moderately differentiated), with prominent keratinization. Invasive carcinoma was focally present at the deep surgical margin in an area that had been treated with heavy cryotherapy. Due to this finding, the patient was advised to have additional plaque radiotherapy for management of potential scleral invasion. Poor follow up and underlying health issues caused delay in obtaining treatment.

In February 2018, orbital MRI revealed an enhancing soft tissue mass inferior to the eye, touching the lateral rectus muscle. We advised surgical resection and radiotherapy, but the patient declined further treatment, again because of his health and family issues.

In April 2018, he experienced severe loss of vision to light perception and ocular pain. Examination revealed iris neovascularization and vitreous hemorrhage with no view of the fundus. There was scleral melting with neovascular glaucoma and exposure of the uvea at the temporal limbus. We suspected tumor recurrence with invasion of the globe. Enucleation was advised.

Gross description: Gross examination revealed massive tumor extending through the eye temporally with exposed uvea at 9:00 o' clock. Transillumination demonstrated a shadow corresponding to the epibulbar mass. Evaluation of the intraocular contents demonstrated a shallow anterior chamber and focally closed

mass. Evaluation of the intraocular contents demonstrated a shallow anterior chamber and focally closed anterior chamber angle with flattening of the iris surface compatible with iris neovascularization. Patchy white discoloration was noted in the region of the ciliary body and anterior choroid suspicious for involvement by tumor. The overlying retina was focally detached by shallow serous detachment. A posterior chamber intraocular lens implant was identified within the partially subluxed lens capsular bag, associated with Soemmering ring cataract formation.

Microscopic description: The temporal limbal epibulbar surface contained a moderately to poorly differentiated carcinoma with prominent surface parakeratin and keratin pearls. The tumor invaded the adjacent corneal and scleral stroma. It extended into the anterior chamber in the vicinity of the full-thickness corneoscleral limbal defect, and was present as a neoplastic membrane on the surface of the iris and ciliary body. The neoplastic cells extended to involve the temporal stroma of the ciliary body and anterior choroid, where the tumor exhibited prominent keratinization and focal cysts containing degenerated keratinized debris.

One iris leaflet was prolapsed into the corneoscleral limbal perforation and was surfaced by the dysplastic epithelium. Rare goblet cells were identified in the invasive tumor, highlighted with PAS, PAS/post-diastase, and Alcian blue stains. Florid iris neovascularization was present. The capsular bag was subluxed and contained cataractous equatorial cortical material. The remaining uveal tract showed extensive detachment, suggestive of prior effusion. The retina was chronically detached by shallow subretinal fluid, with papillary hypertrophy of the underlying retinal pigment epithelium. The vitreous was posteriorly detached, and incorporated scattered lymphocytes and macrophages. The optic nerve was mildly to moderately atrophic.

Diagnosis: Conjunctival mucoepidermoid carcinoma with invasion of the anterior chamber, iris, ciliary body, and choroid.

Discussion

The conjunctiva can give rise to a number of benign and malignant tumors. The most common malignant tumors are melanoma, squamous cell carcinoma (SCC), and lymphoma. Conjunctival SCC can be localized to the epithelium as conjunctival intraepithelial neoplasia (CIN) or can be invasive beneath the epithelium into the stroma as SCC. Both can be treated by surgical excision and/or topical medications. The prognosis is usually excellent.

There is a rare variant of conjunctival SCC, termed mucoepidermoid carcinoma, that has a more aggressive clinical course and worse prognosis. Mucoepidermoid carcinoma appears as a gelatinous conjunctival mass, occasionally with intralesional cysts. It is believed to arise from a conjunctival stem cell that differentiates toward goblet cells. This malignancy can show aggressive behavior and invasion of the adjacent structures. Although locally aggressive, metastasis to distant organs is uncommon. Several cases of mucoepidermoid carcinoma have been reported in the literature and at ophthalmic pathology meetings.

The clinical diagnosis of mucoepidermoid carcinoma can present a diagnostic and therapeutic challenge. While this lesion frequently presents at the limbus as a nodular, papillomatous, gelatinous or leukoplakic growth, raising suspicion for standard SCC, it can also arise in non-limbal location and may lack appreciable tumefaction and distinct margins. Lack of clinical suspicion for malignancy and the poorly defined tumor margins both account for high frequency of incomplete excision and tumor recurrence as occurred in this case. In addition, conjunctival mucoepidermoid carcinoma is biologically more aggressive than standard conjunctival squamous cell carcinoma, frequently presenting with a rapid recurrence (< 6 months following surgery) and with locally invasive behavior, leading to intraocular and orbital invasion as occurred rapidly in this case.

Histopathologically, mucoepidermoid carcinoma is composed of cells with epithelial and goblet cell differentiation, containing intracytoplasmic and extracellular mucin, forming malignant mucinous cysts, and cells with squamous (epidermoid) differentiation, containing identifiable intercellular bridges and focal keratin production. There is typically prominent nuclear anaplasia and mitotic activity. Frequently, the lesions

demonstrate biphasic growth pattern, with the conjunctival component lacking appreciable mucin and demonstrating prominent squamous differentiation, and the deeper invasive component demonstrating more characteristic epithelial and goblet cell differentiation. The reverse can be also observed (mucoepidermoid differentiation in superficial component and squamous differentiation in a deeper component). Additionally, mucoepidermoid differentiation may become more apparent in recurrent lesions or, conversely, the recurrent lesions may lack the previously observed mucoepidermoid differentiation. Thus, careful histopathologic evaluation of biopsied tissue and ancillary stains for mucin are necessary to ensure the accuracy of histopathologic diagnosis. Recent studies also suggest that immunohistochemical panel with antibodies for MUC 19, CK7, EMA, CEA and ki-67 may be helpful in diagnostically-challenging cases.

Given the propensity for locally aggressive biologic behavior, complete surgical excision with wide margin and adjuvant cryotherapy are recommended for conjunctival mucoepidermoid carcinoma. Adjuvant topical chemotherapy with interferon-alpha 2b and mitomycin-C has been also employed intraoperatively and post-operatively in eyes with residual intraepithelial disease.

The histologic resemblance of the conjunctival mucoepidermoid carcinoma to the salivary gland counterpart makes it tempting to apply a uniform grading system for these tumors. When applying the salivary gland mucoepidermoid carcinoma grading to the conjunctival mucoepidermoid carcinoma, the conjunctival lesions tend to be higher grade due to more appreciable squamous differentiation and solid growth pattern. However, despite these higher grade histologic characteristics and locally aggressive growth pattern, frequently leading to loss of vision and an eye, conjunctival mucoepidermoid carcinoma does not appear to have aggressive systemic biologic behavior. There have been only 2 reports of regional metastases and no reports of tumor-related mortality from conjunctival mucoepidermoid carcinoma. This discrepancy between the tumor grade and behavior when comparing the conjunctival and salivary mucoepidermoid carcinomas may stem from the differences in tumor size, location, and the potentially distinct genetic alterations.

In conclusion, we present a case of mucoepidermoid carcinoma of the conjunctiva that grew rapidly and caused loss of vision and loss of eye. A high index of suspicion by both surgeons and pathologists is needed to appropriately diagnose and treat this relatively rare conjunctival tumor.

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