**Eastern Ophthalmic Pathology Society**

**September 13-15; Washington, D.C.**

Vivian Lee, MD Material distributed:

Scheie Eye Institute 1 glass slide

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Shields Oncology Service

“Recurrent eyelid lesion”

Clinical history and course:

A 56-year-old white male presented to the Wills Eye Hospital (WEH) Ocular Oncology Service with a right lower lid mass initially noted in January 2017. An incisional biopsy was performed at that time, which revealed a moderately differentiated, keratinizing squamous cell carcinoma (SCC) with perineural invasion. He underwent an excisional biopsy with frozen sections for margin control. Nine months later, fullness was noted near the right caruncle, and an incisional biopsy was performed, which revealed again invasive keratinizing SCC. An excisional biopsy was performed, which is the specimen distributed here.

Grossly, the main lesion measured 16 x 24 x 28 mm, composed of the medial eyelids and anterior orbit. There was a central scar and firm underlying central nodule. The lacrimal canaliculus was present in the medial aspect of resection. The specimen was serially sectioned perpendicular to the eyelid margin, which revealed a central tan, firm, lobulated mass, measuring 23 x 13 x 13 mm. The mass appeared to abut the medial and lateral resection margins, and was 1-2 mm from the inferior resection margin.

Microscopic examination of hematoxylin-eosin (H&E) stained sections reveal medial eyelids and anterior orbit. A moderately differentiated, invasive carcinoma with predominantly squamous differentiation and prominent keratinization is seen arising primarily from the conjunctival surface. Aggregates, as well as individual, goblet cells are identified focally in tumor nests, highlighted with PAS, PAS/D, and Alcian blue stains. Associated with these areas are epithelial cells that lack definitive squamous differentiation, suggestive of intermediate cells in salivary gland mucoepidermoid carcinoma. Neoplastic cells undermine the lacrimal canaliculus with a focus of secondary involvement of canalicular epithelium; in addition, the tumor extends to the underlying skeletal muscle and orbital fibroadipose tissue. Multiple foci of perineural invasion are identified, but no definitive lymphovascular invasion is seen. The tumor, which measures 12 mm in greatest thickness, is present at the superior and inferior peripheral surgical margins of the main specimen and less than 1 mm from the medial surgical margin. A diagnosis of mucoepidermoid carcinoma (adenosquamous carcinoma) is made.

Discussion:

Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands in adults and children.1,2 It is considered a variant of squamous cell carcinoma (SCC), composed of both epidermoid (squamous) and mucus secreting cells of varying proportions.3 Ocular associated MEC, however, is extremely rare with only 23 cases reported in the literature.2,3 It has been documented in the conjunctiva, eyelids, lacrimal gland, and lacrimal sac.2,3 The term MEC was first devised by Stewart, Foot, and Becker in 1945, though earlier descriptions could be found in the literature as early as 1895.1,4 The histologic criteria established by Stewart et al. for MEC includes the presence of: 1) epidermoid (squamous) cells without requiring the presence of intercellular bridges and epithelial pearls, and 2) cells containing mucus as proved by mucicarmine staining.4 A third type of cell, referred to as intermediate or basal cell, has also been described in this tumor;1,4 and less frequently, hydropic and oncocytic cells have also been observed.4 In regards to the eye, specifically MEC arising from the conjunctiva, Rao and Font were the first to describe a series of five cases in 1976.11 Brownstein,2,5 Albert,6 Jakobiec,4 Shields7 and Eagle7 have all described cases as well.

Clinically, MEC is difficult to distinguish from SCC unless there is an abundance of intracystic and interstitial mucus within the tumor lending itself to a softer and fleshier appearance.3,8 Average age is typically between 52 and 67 years of age;2 and the tumor has been well documented to arise in patients with systemic immune and autoimmune diseases.3,4 Though similar in clinical presentation, it is very important to distinguish MEC from SCC because of the much more aggressive clinical course of MEC.2 Lesions can be locally invasive, and have a recurrence rate between 84% to 100% with nearly all of the cases in the ophthalmic literature recurring within 6 months.2

Histologically, MEC resembles SCC as well, but with the presence of mucus secreting cells.1,3 Because the normal conjunctiva is made up of stratified squamous epithelial cells and mucus-producing goblet cells, Rao and Font speculated that the tumor arises from neoplastic differentiation along both directions.1 Mucin-producing cells may have a classic signet ring or bloated columnar appearance,11 while keratin pearls and dyskeratosis are rare, unlike in this case.3 Jakobiec et al. performed electron microscopic studies of their case of MEC, and identified mucus granules within squamous cells that did not look morphologically like goblet cells.4 Interestingly, they also noted focal myofilamentary differentiation in the basal cells of areas where their tumor formed tubular structures.4 In normal conjunctival basal cells, myofilamentary differentiation is usually absent, but can be found in the basal ductal cells of the lacrimal gland.4 Histochemical stains for mucin, such as alcian blue and mucicarmine, assist in highlighting intracellular mucin, which is resistant to hyaluronidase digestion.1 In cases of discrete mucus production, such stains are required in histopathologic evaluation of tumors suspicious for MEC in order to identify minute foci of intracellular mucin.2,4,5 Brownstein et al. found that the combination of mucicarmine, colloidal iron, alcian blue, mucin-1, and CEA was highly sensitive and specific; and of the group, mucicarmine was the single best stain for the diagnosis of MEC.2 Additionally, CK7 immunostaining may be helpful in distinguishing MEC from SCC since CK7 positivity may be indicative of mucoepidermoid differentiation; and therefore, may be useful in revealing potentially neoplastic cells.3 Because conjunctival SCCs are usually CK7 negative,3 if scattered CK7 positive cells are observed in an area of SCC in-situ, this may warrant further examination for evidence of MEC. MUC 19 may also be preferentially expressed in MEC, and may be an useful adjunct stain.3

Studies based on salivary gland tumors have divided MEC into three categories: low grade lesions (92 to 100% 5-year survival), intermediate grade (62 to 92%), and high grade (0 to 43%). However, recent studies have shown no significant difference in disease free state or mortality between low and intermediate grades.9 Criteria for classification are summarized in Table 1.10 In a retrospective study from MD Anderson, positive lymph nodes, extracapsular lymph node spread, and perineural invasion were found to be poor prognostic indicators, while advanced disease stage and perineural invasion were found to be most significant on multivariate analysis.9 While salivary gland MECs are associated with distant metastasis and death, conjunctival MECs are associated only with frequent recurrence, local invasion, local metastases,9 and rarely distant metastases, and thus far no deaths.3,8 Interestingly, conjunctival MEC typically exhibits higher grade of cytologic features, such as fewer mucus producing cells and cystic spaces; but because total volume is usually smaller compared to salivary gland MEC, this aspect probably lends itself to better overall prognosis.3 Interestingly, a chromosomal translocation in a large subset of salivary gland MEC has been found, MECT1-MAML2 [t(11;19)(q14-21;p12-13)], that has been associated with low grade histopathologic features and a favorable clinical prognosis.11 This translocation induces a fusion protein that serves as a transcription activation factor in cAMP/CREB and Notch pathways.11,12 However, recent studies have challenged its prognostic significance, especially given the fact that over 50% of high grade tumors have been found to harbor this translocation;12 and instead, have proposed that MECT1-MAML2 negative tumors be categorized as a separate tumor.12 A recent abstract examined 11 cases of conjunctival MEC and found no chromosomal translocation, which suggests the possibility of that conjunctival MECs may also represent a separate type of tumor.13

At a minimum, wide local excision is recommended.2 Other additional treatments, such as alcohol corneal epitheliectomy, cryotherapy to the margins and base, radiation therapy, and adjuvant chemotherapy have also been proposed to reduce the risk of recurrence.3,7,14 Nevertheless, treatment depends on accurate diagnosis. Therefore, it is recommended that all atypical SCC should be re-evaluated with alcian blue or mucicarmine stains with deeper levels of sectioning.2–4 Lastly, close clinical follow-ups every 3 months for 12-18 months is highly recommended given the high recurrence rates for MEC.3

Table 1.

From salivary gland tumors:

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| --- | --- |
| Low grade: 15% recur, 5 year survival 90 - 98%, usually stage I  High grade: 25% recur, 5 year survival 50 - 56%, deaths usually within first 5 years  Note: significant grading disparity exists between pathologists (Am J Surg Pathol 2001;25:835) |  |
| AFIP point system:  2 points if < 20% intracystic component  2 points if neural invasion  3 points if necrosis  3 points if 4+ mitotic figures/10 HPF  4 points if anaplasia | Low grade if total score is 0 - 4 points  Intermediate grade if  5 - 6 points  High grade if 7+ points |
| TNM staging for malignant salivary tumors  T0: No evidence of primary tumor  T1: Tumor < 2 cm without extraparenchymal spread  T2: Tumor 2-4 cm, without extraparenchymal extention  T3: Tumor > 4 cm or with extraparenchymal spread but no facial nerve spread  T4: T4a: Spread to facial nerve, skin, mandible, ear canal  T4b: Spread to base of skull, pterygoid plates, encased external carotid artery |  |

Poor prognostic factors: older age, male, submandibular gland, extraglandular extension, vascular invasion, necrosis, high mitotic rate, high histologic grade

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