Ocular Oncology and Pathology

Mucoepidermoid Carcinoma of the Lacrimal Sac: Clinical-Pathologic Analysis, Including Molecular Genetics

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Abstract

Purpose: The aim of this study was to assess whether mucoepidermoid carcinoma of the lacrimal sac is a counterpart of *CRTC1/3-MAML2* gene fusion-related salivary gland mucoepidermoid carcinoma. *Methods:* In this retrospective observational case series, pathology records were searched for all cases of lacrimal sac mucoepidermoid carcinoma diagnosed between 1990 and 2018. Data collected included demographics, clinical findings, management, and follow-up. Pathologic parameters assessed included tumor morphology, immunohistochemistry, and *MAML2* and *EGFR* fluorescence in situ hybridization (FISH) studies. *Results:* Six patients with mucoepidermoid carcinoma of the lacrimal sac, 5 males and 1 female, with a median age of 63 years (range 24–66) were identified. Five tumors were managed with radical resection and 1 patient underwent orbital exenteration. None of the patients developed recurrence or metastases with an average follow-up of 18 months (range 13–23). All tumors had morphologic and immunohistochemical features of mucoepidermoid carcinoma and overexpressed EGFR. *MAML2* FISH was negative for *MAML2* rearrangement in all tumors. *EGFR* FISH demonstrated *EGFR* amplification in 1 tumor. *Conclusions:* Mucoepidermoid carcinoma of the lacrimal sac is not a lacrimal sac counterpart of *CRTC1/3-MAML2* gene fusion-related salivary gland mucoepidermoid carcinoma. *EGFR* pathway activation and *EGFR* amplification in a subset of these neoplasms suggest the potential role for anti-EGFR agents.

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Introduction

Mucoepidermoid carcinoma of the lacrimal sac is a rare locally aggressive malignancy, with <20 cases reported in the literature [1–8]. Analogous to its salivary gland counterpart, mucoepidermoid carcinoma of the lacrimal sac, nasal cavity, and paranasal sinuses is composed of epidermoid, mucus-secreting, and intermediate cells and is presumed to originate predominantly from the mucosal mucoserous glands and less frequently from the over-

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lying epithelium [1, 2, 9–11]. Recent studies from the salivary gland literature have documented recurrent translocations involving mastermind-like protein 2 (*MAML2*) and CREB-regulated transcription coactivator 1 (*CRTC1*) or *CRTC3* genes, resulting in *CRTC1/3-MAML2* gene fusion in 34–81% of mucoepidermoid carcinomas [12–15]. The *MAML2* translocation status has gained recognition for its diagnostic utility as an objective confirmation of mucoepidermoid carcinoma diagnosis, particularly in tumors with overlapping histology [12–14]. Additionally, *MAML2* translocation in salivary gland carcinomas has been traditionally associated with a lower histologic grade, less advanced clinical stage, and longer disease-free and overall survival [15, 16]. With increasing emphasis on targetable therapy, identification of the *CRTC1/3-MAML2* fusion product may emerge as a potential therapeutic target. Finally, mucoepidermoid carcinomas have been shown to demonstrate epidermal growth factor receptor/extracellular receptor kinase (EGFR/ERK) pathway activation, which may be influenced by *CRTC1/3-MAML2* fusion and *EGFR* gene copy number alterations, suggesting the role for EGFR and mitogen-activated protein kinase pathway inhibitors [13, 16, 17].

The role of *MAML2* gene rearrangement, *EGFR* gene copy number alterations, and EGFR pathway activation in the mucoepidermoid carcinoma of the lacrimal sac has not been systematically explored. Herein, we describe clinical-pathologic characteristics of 6 lacrimal sac mucoepidermoid carcinomas, with a focus on *MAML2* and *EGFR* status.

Materials and Methods

The Wills Eye Hospital Institutional Review Board approved this study. The study was performed in compliance with HIPAA guidelines and with the tenets of the Declaration of Helsinki.

Patient Selection
Wills Eye Hospital Pathology records were searched for all cases of mucoepidermoid carcinoma of the lacrimal sac diagnosed between 1990 and 2018. Medical records of identified patients were reviewed. Data collected included patients' age, sex, presenting symptoms and their duration, clinical and imaging findings at presentation, management, and follow-up information. Because lacrimal sac carcinoma does not have specific American Joint Committee on Cancer (AJCC) staging guidelines, the tumors were staged based on the AJCC 8th edition guidelines for carcinoma of the nasal cavity and paranasal sinuses [18].

Histopathology
Routine sections stained with hematoxylin-eosin, periodic acid-Schiff (PAS), Alcian blue, and Hale's colloidal iron were pre-

pared from paraffin-embedded, formalin-fixed tissues. Morphologic parameters assessed included the presence of an intraepithelial or intraglandular in situ component, constituent cell types (epidermoid, intermediate, and mucocytes), perineural invasion, local extent of disease, pathologic staging (based on the AJCC 8th edition, carcinoma of the nasal cavity and paranasal sinuses guidelines) [18], and tumor grading in accordance with the AFIP grading system for mucoepidermoid carcinoma of the salivary glands (low-grade = score 0–4, intermediate grade = score 5–6, high-grade = score >6; score components: intracystic component <20% = score 2, neural invasion = score 2, mitosis ≥4/10 high power fields = score 3, necrosis = score 3, anaplasia = score 4) [19].

Immunohistochemistry
The immunostaining was performed with the following primary antibodies: monoclonal mouse anti-human cytokeratin 7 (CK7; prediluted; DAKO, CA, USA), monoclonal mouse anti-human CK20 (prediluted; Biocare, CA, USA), monoclonal mouse anti-human p63 (prediluted; Biocare), and monoclonal mouse anti-human EGFR (Clone H11, 1:50; DAKO). Peroxidase activity was visualized by applying diaminobenzidine solution containing 0.05% H_2O_2. Sections were counterstained with a modified Mayer's hematoxylin, dehydrated, cleared, and mounted. Appropriate positive and negative controls were run with each batch. All immunohistochemical stains were prepared on Leica autostainer BOND III in accordance with the manufacturer's instructions.

Immunohistochemical stains for CK7, CK20, and p63 were scored semi-quantitatively based on the strength of cytoplasmic (CK7 and CK20) and nuclear (p63) expression (0 = no staining, 1+ = weak staining, 2+ = moderate staining, 3+ = strong staining) and based on the percentage of immunoreactive cells (0% = 0, 1–25% = 1+, 26–50% = 2+, 51–75% = 3+, 76–100% = 4+). Because of heterogeneity in methodology for EGFR expression assessment, we evaluated EGFR expression by 3 methods: (1) as percentage of immunoreactive cells with membranous and cytoplasmic staining, (2) semi-quantitatively (0, no positive cells; 1+, low discontinuous membrane staining; 2+, unequivocal membrane staining with moderate intensity; and 3+, strong and complete membrane staining), as described by Lujan et al. [17], and (3) by an H-score (defined as a continuous variable with a scale ranging from 0 to 300 and calculated using the following formula: 1 × [percentage of weakly stained cells, 1+] + 2 × [percentage of moderately stained cells staining, 2+] + 3 × [percentage of strongly stained cells, 3+] [range 0–300]), as described by Avilés-Salas et al. [20]. EGFR overexpression was defined as 2+ (moderate membranous staining) and 3+ (strong and complete membranous staining) in >10% of neoplastic cells [17] or H-score of >100 [20].

Fluorescence in situ Hybridization Studies
After the areas for cell counting were determined by a hematoxylin-eosin slide review, a 4-μm-thick section of formalin-fixed paraffin-embedded tissue was placed onto a positively charged slide.

Fluorescence in situ Hybridization for Detection of *MAML2* Gene Rearrangement
The *MAML2* fluorescence in situ hybridization (FISH) assay was performed with the probe Zytolight SPEC MAML2 Dual Color Break Apart Probe (11q21; ZytoVision, Bremerhaven, Germany) and the Histology FISH Accessory Kit (ZytoVision) in accor-

dance with the manufacturer's protocols. At least 40 randomly selected nonoverlapping tumor cell nuclei were evaluated for the presence of yellow (normal) or green and red (chromosomal break-apart) fluorescent signals at ×1,000 magnification. The sample was considered positive for rearrangement when >20% of nuclei showed break-apart signals. *CRTC1/3-MAML2* fusion gene-positive salivary gland mucoepidermoid carcinoma cases were used as a positive control. The *MAML2* FISH assay was internally validated on 70 salivary gland mucoepidermoid carcinomas and 40 other (nonmucoepidermoid carcinoma) epithelial salivary gland tumors.

FISH for Detection of *EGFR* Gene Copy Number Alteration

The *EGFR* FISH assay was carried out with the EGFR (11p11.2) SpectrumOrange/Con 7 (11q11.1) SpectrumGreen probe (Empire Genomics, NY, USA) in accordance with the manufacturer's protocols. Four physically distant tumor areas were selected and the *EGFR* and Con 7 (centromeric control) signals were counted in 40 tumor nuclei at ×1,000 magnification, and the proportion of *EGFR*/Con 7 signal number was calculated. The cases were considered normal if 2 blue and 2 red signals were visualized in each nucleus. Polysomy was considered where 3 or more blue and red signals (in equal number) were seen in each nucleus. The *EGFR* amplification was defined as EGFR/Con 7 ratio of >2.0. The *EGFR* FISH methodology was adopted from the FDA-approved FISH assay for the *Her2* family and validated internally.
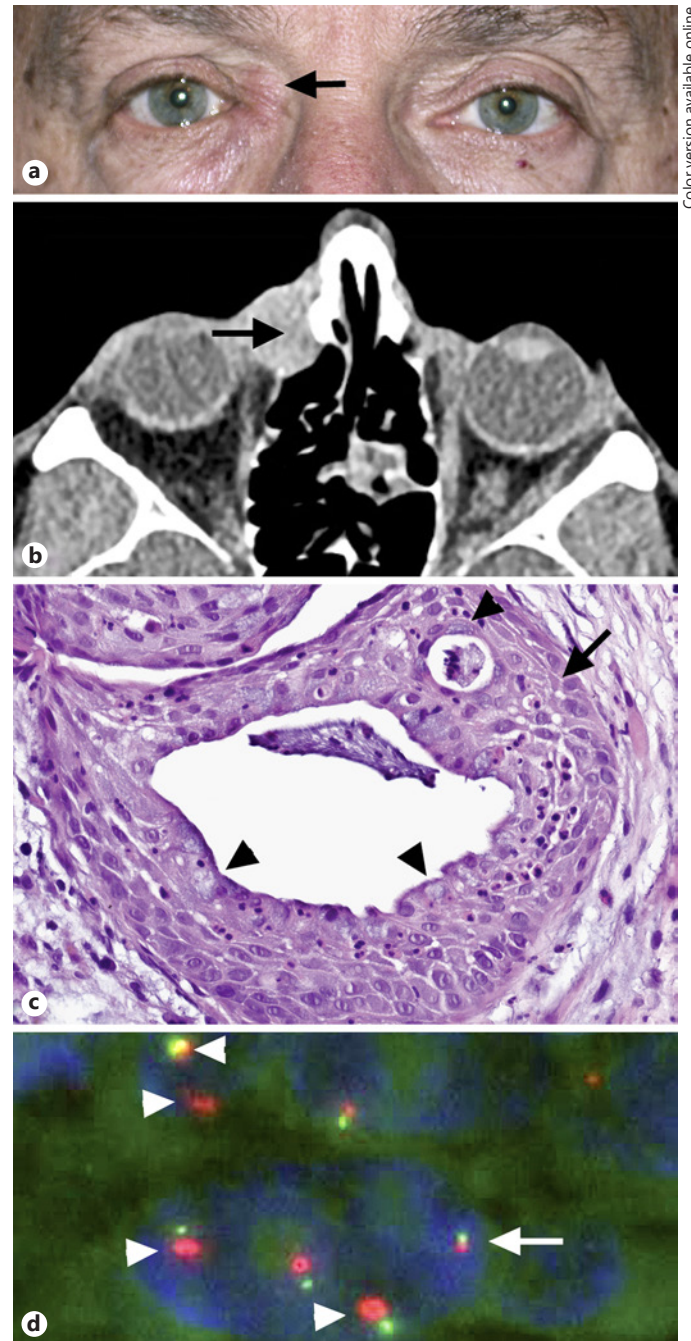
Results

Clinical Characteristics

Review of pathology medical records identified 6 patients with mucoepidermoid carcinoma of the lacrimal sac, 5 males and 1 female, with a median age of 63 years (average 54 months; range 24–66). All patients presented with unilateral right-sided (4/6, 67%) and left-sided (2/6, 33%) epiphora, associated with a palpable mass in the region of the lacrimal sac (4/6, 67%), eye pain or irritation (4/6, 67%), recurrent dacryocystitis (2/6, 33%),

and nasal congestion (1/6, 17%; Fig. 1, 2). Duration of symptoms ranged from 4 to 16 months (average 9 months). Two patients had undergone prior dacryocystorhinostomy for nasolacrimal duct obstruction. Imaging demonstrated a soft tissue mass centered in the lacrimal sac, ranging in size from 1.5 to 2.5 cm (average 2.0 cm; Fig. 1, 2). Five patients (83%) were managed with radical resection of the lacrimal sac and nasolacrimal

Color version available online

Fig. 1. Clinical and pathologic characteristics of lacrimal sac tumor in patient 3. **a** Right medial canthal mass, focally situated above the medial canthal tendon (arrow). **b** Axial post-contrast computed tomography scan demonstrates a mass in the region of the lacrimal sac (arrow), with focal adjacent bony changes and with extension into the medial orbit. **c** Well-differentiated mucoepidermoid carcinoma is composed of epidermoid cells with intercellular bridges (arrow), mucocytes (arrowheads), and cells with intermediate morphology without appreciable nuclear atypia or mitotic activity, forming mucin-filled cysts (stain, hematoxylin-eosin; original magnification, ×100). **d** *EGFR* fluorescence in situ hybridization studies demonstrate amplification of red *EGFR* signal (arrowheads), which is 2–4 times the size of the green centromeric (Con 7) signal in neoplastic cell nuclei, compatible with an *EGFR*/Con 7 ratio of >2. In contrast, the cell nucleus without EGFR amplification features *EGFR* and centromeric signals of similar size (arrow).

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duct system and varying portions of the adjacent orbital tissue, maxillary sinus, and ethmoid sinus. One patient (17%) with extensive orbital soft tissue involvement underwent orbital exenteration. All resections were performed with frozen section control of margins. Postoperative radiation therapy was delivered to 4 (67%) patients. Follow-up information was available on 4 of 6 patients (67%). None of the patients developed recurrence or metastases with an average follow-up of 18 months (range 13–23). The clinical characteristics of the patients are summarized in Table 1.

Histopathology and Immunohistochemistry

Histopathologic and immunohistochemical features of the 6 lacrimal sac mucoepidermoid carcinomas are summarized in Table 2. All tumors were composed of varying proportions of epidermoid (nonkeratinizing squamous) cells, mucocytes (goblet-like cells), and intermediate cells (basal or cuboidal cells with morphology in-between mucocytes and squamous cells), forming cystic structures filled with mucin (Fig. 1c). Solid tumor nests were conspicuous in higher grade tumors (Fig. 2c). The intracytoplasmic mucin in mucocytes and extracellular mucin was highlighted with PAS, Alcian blue, and Hale's colloidal iron stains (Fig. 2d). Notably, no keratinization (squamous pearl formation) was identified. An association with the overlying dysplastic lacrimal sac epithelium was observed in 2 (33%) tumors. No definitive in situ component was identified in the other 4 (67%) tumors. Perineural invasion was documented in 2 (33%) tumors. Four (67%) tumors were of intermediate histologic grade (grade 2), and 2 tumors (33%) were low-grade (grade 1).

Immunohistochemical studies showed that all tumors moderately or strongly expressed CK7 (25–100% of cells) and strongly expressed p63 (75–100% of cells). CK20 was focally weakly to moderately expressed in 2 of 6 (33%) tumors. EGFR was overexpressed in all neoplasms. EGFR expression appeared as moderate-to-strong, membranous, circumferential staining in 50% or more cells in all tumors and in 80% or more cells in 5 of 6 (83%) tumors (Fig. 2e). H-score was ≥100 in all tumors (median 225; average 222; range 120–290).

MAML2 and EGFR FISH

MAML2 FISH was negative for rearrangement in the *MAML2* gene in all tumors. *EGFR* FISH demonstrated amplification in *EGFR* gene (3.8 EGFR signals/cell; EGFR/Con 7 ratio 2.02) in 1 tumor and no evidence of polysomy in any of the tumors.
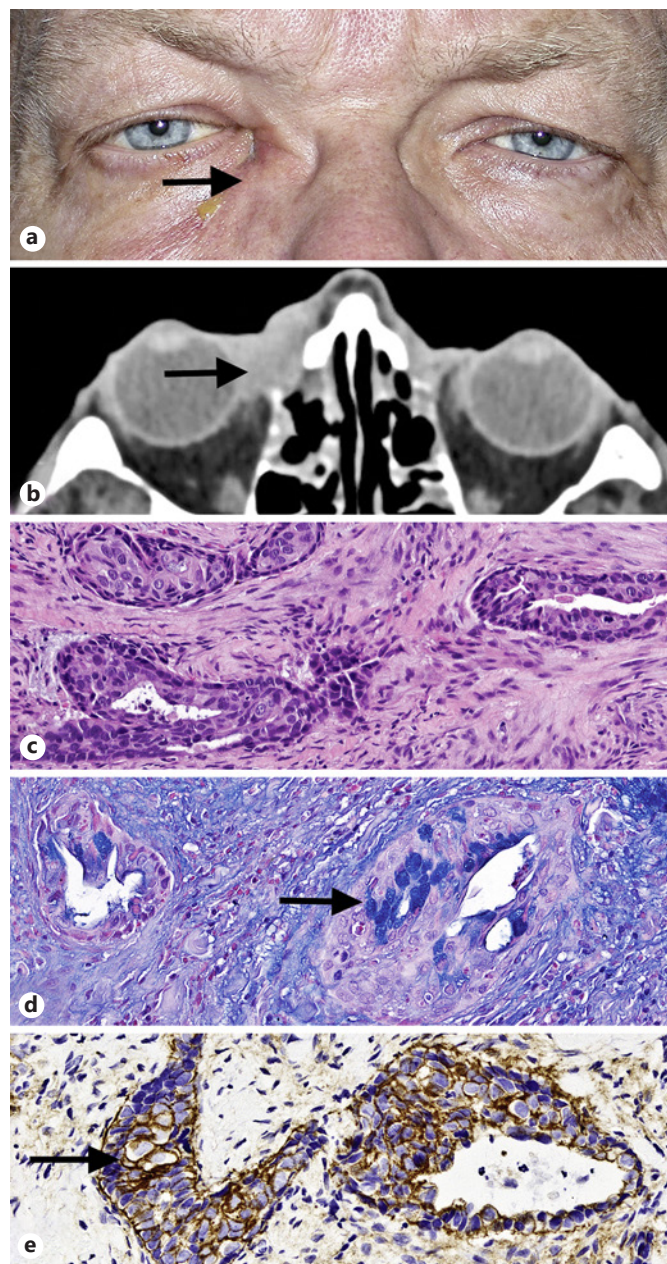
Fig. 2. Clinical and pathologic characteristics of lacrimal sac tumor in patient 5. **a** Right medial canthal mass (arrow). **b** Axial postcontrast computed tomography scan demonstrates a mass in the region of the lacrimal sac (arrow), with focal bone destruction and with extension into the medial orbit. **c** Invasive neoplasm, composed predominantly of nonkeratinizing epidermoid cells and intermediate cells, without readily identifiable mucocytes forms solid nests and cysts in a background of markedly desmoplastic stroma. **d** Alcian blue highlights the intracytoplasmic mucin in mucocytes (arrow). **e** Intense membranous staining with EGFR (arrow) is present in most neoplastic cells. (stains: **a**, hematoxylin-eosin; **b**, Alcian blue; **c**, EGFR; **a–d**, original magnification, ×50).

Table 1. Clinical features and staging of patients with lacrimal sac mucoepidermoid carcinoma

Patient	Age, years/ sex	Laterality	Presenting symptoms (duration in months)	Imaging findings (CT scan)	Secondary sites of involvement[a]	pT[b]	cN[b]	cM[b]	Stage[b]	Surgical management	Adjuvant therapy	Recurrence or metastases, follow-up in months
1	45/M	Left	Epiphora and recurrent dacryocystitis (12 months)	2.5-cm soft tissue mass at medial canthal area, associated with globe displacement	Inferomedial orbit, nasal cavity, ethmoid sinus	3	x	x	At least III	LS and NLD resection, lateral rhinotomy, ethmoidectomy, medial maxillectomy, orbital exenteration	XRT	N/A
2	24/M	Right	Ephiphora (9 months), LS mass (4 months)	N/A	Nasal cavity, medial orbit	3	x	x	At least III	LS and NLD resection, medial orbital tissue resection	None	N/A
3	62/M	Right	Epiphora, recurrent dacyocystitis, LS mass, pain (16 months)	1.9-cm LS mass with erosion of lacrimal bone and bony lacrimal duct	Maxilla, medial orbit	3	0	0	III	LS and NLD resection, ethmoidectomy, medial maxillectomy, middle and inferior turbinectomy	None	No, 23 months
4	66/F	Left	Epiphora, LS mass, eye irritation, nasal congestion (10 months)	1.6-cm soft tissue mass in LS without bony erosion	Nasal cavity	1	0	0	I	LS and NLD resection, medial maxillectomy, ethmoidectomy, anterior turbinectomy	XRT	No, 20 months
5	65/M	Right	Epiphora, eye pain (6 months)	2.5-cm soft tissue mass in LS	Maxilla, medial orbit	3	0	0	III	LS and NLD resection, medial maxillectomy	XRT	No, 13 months
6	63/M	Right	LS mass, pain (6 months)	1.5-cm soft tissue mass in LS with bony changes	Maxilla, medial orbit	3	0	0	III	LS resection, medial maxillectomy	XRT	No, 17 months

CT, computed tomography; NLD, nasolacrimal duct; LS, lacrimal sac; x, not available; N/A, not available; pT, pathology tumor grouping by size; cN, clinical documentation of nodal metastasis; cM, clinical documentation of distal metastasis; XRT, external beam radiotherapy. [a] Based on imaging studies with pathologic confirmation. [b] TNM classification and stage groupings are adopted from the AJCC classification of carcinoma of the nasal cavity and ethmoid sinus (patients 1, 2, and 4) and maxillary sinus (patients 3, 5, and 6), 8th edition [18].

Table 2. Pathology features of lacrimal sac mucoepidermoid carcinoma

Patient	In situ component	Grade (AFIP)[a]	Perineural invasion	CK7	CK20	p63	EGFR IHC[b] %, S, H-score	EGFR FISH	MAML2 FISH
1	Yes	G2	No	+	–	+	80, 2+, 190	Negative	Negative
2	Yes	G2	No	+	–	+	80, 3+, 210	N/A	Negative
3	N/A	G1	No	+	–	+	50, 2+, 120	Positive	Negative
4	N/A	G1	No	+	–	+	98, 3+, 290	Negative	Negative
5	N/A	G2	Yes	+	+	+	90, 3+, 240	Negative	Negative
6	N/A	G2	Yes	+	–	+	90, 3+, 280	Negative	Negative

CK, cytokeratin; EGFR, Epidermal Growth Factor Receptor; FISH, fluorescence in situ hybridization; MAML2, Mastermind Like Transcriptional Coactivator 2 gene; N/A, not available or unable to assess; (+), positive; (–), negative. [a] AFIP grading system for mucoepidermoid carcinoma of salivary glands [19]. [b] EGFR IHC, immunohistochemical expression of EGFR staining is scored by 3 methods: (1) %, percentage of immunoreactive cells with membranous and cytoplasmic staining; (2) S, semi-quantitative assessment (0, no positive cells; 1+, low discontinuous membrane staining; 2+, unequivocal membrane staining with moderate intensity; and 3+, strong and complete membrane staining; only cases with 2+ and 3+ staining patterns in >10% of tumor cells were considered positive) as described by Lujan et al. [17]; (3) H-score (EGFR H-score was defined as a continuous variable with a scale ranging from 0 to 300 and was calculated using the following formula: $1 \times$ [percentage of weakly stained cells, 1+] + $2 \times$ [percentage of moderately stained cells staining, 2+] + $3 \times$ [percentage of strongly stained cells, 3+] [range 0–300]) as described by Avilés-Salas et al. [20].

Discussion

Mucoepidermoid carcinoma is the most common salivary gland malignancy, composed of 3 cell types: goblet cell-like mucocytes, epidermoid cells, and intermediate cells [12, 14]. Mucoepidermoid carcinoma can infrequently involve the lacrimal sac, where this neoplasm affects predominantly males between the 4th and 6th de-

cades, presenting with signs and symptoms of nasolacrimal duct obstruction and a mass in the lacrimal sac region – a pattern that was also seen in our patients [1–8].

During the past decade, a translocation involving the *CRTC1* gene at 19p13 and the *MAML2* gene at 11q21 t(11;19)(q21;p13) has gained recognition for its diagnostic utility as an objective confirmation of the diagnosis of salivary gland mucoepidermoid carcinoma [12–15]. Lat-

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er studies revealed that a small subset of mucoepidermoid carcinoma instead harbors a t(11;15)(q21;q26) translocation generating a molecularly similar *CRTC3-MAML2* fusion [12]. In addition to its diagnostic value, the *CRTC1/3-MAML2* gene fusion initially has been associated with a lower histologic grade, a less advanced clinical stage, and longer disease-free and overall survival, suggesting a more indolent subset of mucoepidermoid carcinoma [14, 15]. More recent reappraisal of the prognostic value of the *CRTC1/3-MAML2* gene fusion questioned its prognostic utility, possibly reflecting the use of stricter diagnostic criteria for mucoepidermoid carcinoma and more rigorous exclusion of mucoepidermoid carcinoma mimics, including adenosquamous carcinoma [14, 21].

The evaluation for *MAML2* rearrangement has been incorporated into the diagnostic workup of mucoepidermoid carcinoma of other body sites, such as the lacrimal gland, pulmonary tree, pancreas, and cervix, leading to reappraisal of these tumors [22–25]. *MAML2* status has been found to be helpful in distinguishing mucoepidermoid carcinoma from morphologically similar neoplasms and has led to the suggestion that *CRTC1/3-MAML2*-negative tumors may be more appropriately termed adenocarcinomas or adenosquamous carcinomas with mucoepidermoid carcinoma-like features, a distinction that may have therapeutic and prognostic implications [22–25].

There are limited data on the molecular genetic landscape of mucoepidermoid carcinoma of the lacrimal sac, nasal cavity, and paranasal sinuses. In a study evaluating mucoepidermoid carcinomas from various body sites for *MAML2* translocation, Chiosea et al. [14] documented a *MAML2* rearrangement in 2 of 4 sinonasal tumors. Interestingly, *MAML2* translocation was not identified in 1 recently described lacrimal sac mucoepidermoid carcinoma arising in an inverted Schneiderian papilloma [8]. We similarly did not observe a *MAML2* translocation in any of the tumors in our study. Although all tumors included in this study had the characteristic morphologic features of mucoepidermoid carcinoma and an immunohistochemical profile similar to that previously documented in the sinonasal mucoepidermoid carcinoma (CK7 focal-to-diffuse positive, CK20 negative-to-focal positive, p63 diffuse positive), the absence of *MAML2* rearrangement raises a question regarding the nature of these lacrimal sac tumors [10]. It is possible that, analogous to *MAML2*-negative tumors in other body sites, the term adenosquamous carcinoma with mucoepidermoid carcinoma-like features may be more appropriate for these lesions. This hypothesis is strengthened by the documentation of the lacrimal sac epithelial origin of a subset of previously reported mucoepidermoid carcinomas and of 2 tumors described in this study [2, 8]. The overall rarity of lacrimal sac adenocarcinoma, adenosquamous carcinoma, and mucoepidermoid carcinoma precludes a meaningful comparison of biologic behavior of these tumors.

In addition to *MAML2* translocation, salivary gland mucoepidermoid carcinomas have been shown to demonstrate upregulation of the *EGFR/ERK* signaling pathway. This phenomenon has been attributed to the downstream effect of the *CRTC1/3-MAML2* gene fusion product and to *EGFR* gene copy number alterations [13, 16, 17]. We identified *EFGR* gene amplification in 1 tumor in our study and increased EGFR protein expression in all tumors, suggestive of EGFR pathway activation. Interestingly, 1 recently described lacrimal sac mucoepidermoid carcinoma similarly demonstrated increased EGFR protein expression [7]. However, these events are not specific to mucoepidermoid carcinoma and have been documented in the sinonasal adenocarcinoma [26, 27].

Mucoepidermoid carcinoma of the lacrimal sac has a low risk for metastases and tends to be locally aggressive, with a potential for involvement of vital structures [1–8]. In recent years, orbital exenteration has been largely supplanted by globe-sparing multimodal therapies, including en-block resection of the nasolacrimal system and adjacent sinuses followed by adjuvant radiotherapy and, in some cases, chemotherapy [4, 5, 28]. This management approach is also evident in the care of our patients. The role of targeted therapies for locally aggressive and metastatic lacrimal sac tumors remains to be explored. While our findings suggest that targeted therapy toward *CRTC1/3-MAML2* gene fusion may not be effective for lacrimal sac mucoepidermoid carcinoma, it is possible that anti-EGFR agents might be effective.

Statement of Ethics

This study was approved by the Wills Eye Hospital Institutional Review Board and was performed in compliance with the tenets of the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare. None of the authors have relevant financial relationships with commercial interests.

Funding Sources

Author Contributions

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