Primary Cystadenocarcinoma of the Lacrimal Gland

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Purpose: To report a patient with a cystadenocarcinoma of the lacrimal gland, a tumor not previously described in the ophthalmic literature. Salivary gland cystadenocarcinomas constitute a distinct group of epithelial malignancies characterized by an invasive, predominantly cystic pattern of growth that have an indolent behavior and a low incidence of metastases and recurrences.

Design: Single interventional case report.

Methods: The clinical findings, results of imaging studies, and pathologic findings are presented.

Results: A 67-year-old man presented with a 5-year history of ptosis in the right upper eyelid. A lacrimal fossa tumor was found. The tumor was excised with an intact capsule, and the histopathologic diagnosis was primary cystadenocarcinoma of the lacrimal gland. The patient received no other form of treatment and has been observed for 1 year without evidence of recurrence or metastatic disease.

Conclusions: Until recently, primary adenocarcinomas of the lacrimal gland were not further subclassified. Current knowledge gained from salivary gland tumors indicates that primary adenocarcinoma encompasses a group of tumors with separate morphologic features and varied biologic behavior. *Ophthalmology 2003;110: 2006–2010 © 2003 by the American Academy of Ophthalmology.*

Malignant epithelial tumors of the lacrimal represent approximately 2% to 4% of biopsied or excised lacrimal gland lesions.[1,2] It was not until recently that individual types of lacrimal gland adenocarcinomas, with different biologic behavior ranging from indolent to locally aggressive, were identified.[3–10]

Cystadenocarcinomas of the salivary gland are a distinct, but cytomorphologically diverse, group of malignant epithelial tumors characterized by an invasive, predominantly cystic pattern of growth.[11] Their behavior is relatively nonaggressive. We describe a patient with a cystadenocarcinoma of the lacrimal gland. After total local tumor excision, there were no recurrences or signs of dissemination 1 year after treatment. To the best of our knowledge, this is the first report of this tumor's originating in the lacrimal gland.

Case Report

Clinical History

A 67-year-old male patient was referred for evaluation and treatment of a right lacrimal fossa tumor. He reported no pain or diplopia. He had noticed a progressive right upper lid ptosis for the last 5 years. Examination of a photograph taken 5 years previously showed a mild S-shaped right upper lid ptosis. His medical and ophthalmic history were unremarkable. Best-corrected visual acuity was 20/20 in both eyes. The pupils reacted briskly to light, and there was no afferent pupillary defect. Ductions and versions were complete. The marginal reflex distance was 3 mm for the right upper eyelid and 4 mm for the left, with an S shape for the right lid (Fig 1). Levator function was 15 mm in both eyes. Retropulsion was firm on the right side. Two millimeters of exophthalmos was measured with a Hertel exophthalmometer. A firm, nontender mass was palpable under the right orbital rim in the temporal quadrant. Slit-lamp examination was unremarkable, intraocular pressure was 16 mmHg in both eyes, and funduscopic examination was normal. Computed tomography of the orbits showed a homogeneous, ovoid-shaped, extraconal tumor located in the right lacrimal fossa without bone involvement (Fig 2). There were several calcifications within the tumor. Magnetic resonance imaging revealed two large cystic lesions and several smaller ones occupying most of the tumor in T2-weighted scans (Fig 3). The tumor was excised completely with an intact capsule through a lateral orbitotomy.

Pathologic Findings

Gross examination showed a circumscribed multinodular rubber-like reddish mass measuring 25 × 17 × 12 mm. The tumor was composed of one large cyst and two smaller cysts containing brown exudate and yellowish deposits (Fig 4). Paraffin-embedded sections showed multiple cysts with exudate containing blood and also showed lacrimal gland tissue in one area of the surface of the mass. The cysts were lined by cuboidal epithelial cells with eosinophilic cytoplasm and small, round nuclei (Fig 5). The cells were piled in a pseudopapillary configuration (Fig 6). In other areas, the cuboidal cells were larger and had pleomorphic nuclei, with occasional atypical mitotic figures (Fig 7). The lumen of the cysts was filled by exudate containing detached viable and necrotic neoplastic cells with foci of calcification. Organized exudate with histiocytes was observed. Foci of calcification were also abutted on

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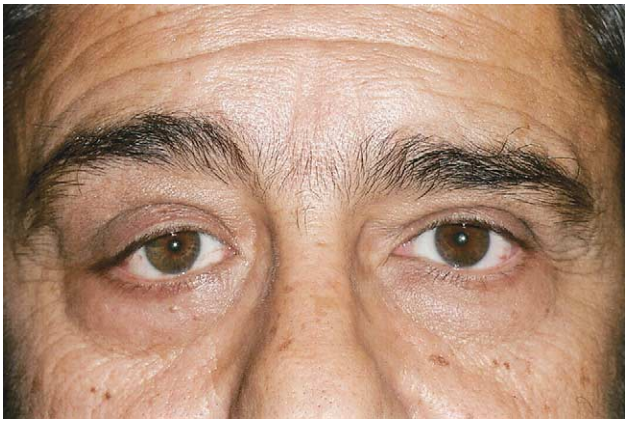

Figure 1. A 67-year-old man with S-shaped ptosis of the right eyelid.

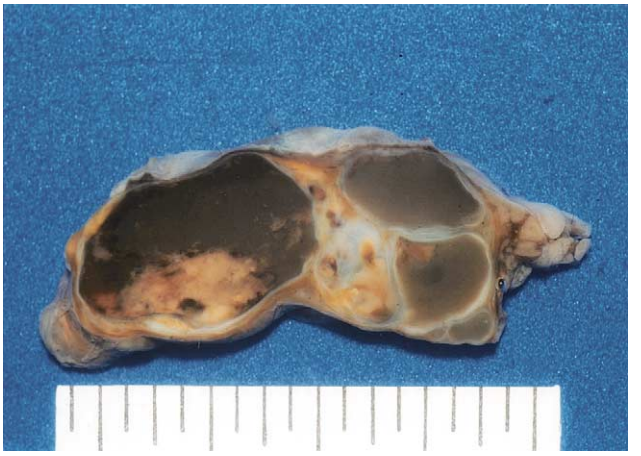

Figure 4. Cut surface of the tumor shows large cysts with brownish exudate.

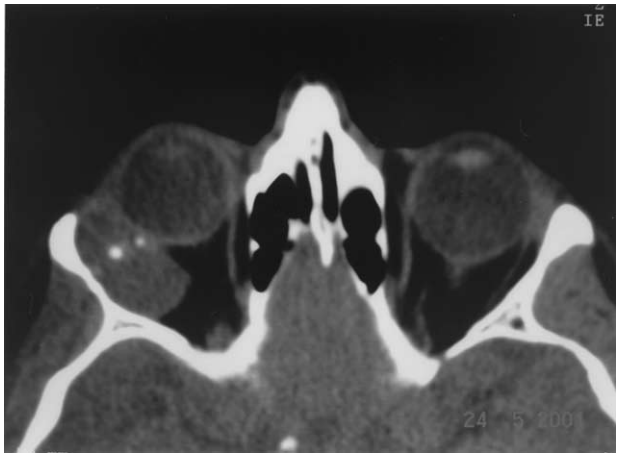

Figure 2. Axial computed tomographic scan of the orbits demonstrates a large homogeneous mass with several foci of calcification involving the lacrimal gland fossa.

the lumen of the cysts, surrounded by a collagenous matrix. In the infiltrative areas, the tumor cells were immersed in a dense collagenous extracellular matrix in which hemosiderin deposits were present (Fig 8). The adjacent lacrimal gland tissue had a normal appearance, with periductal fibrosis and foci of small lymphocytes. The cells did not disclose mucosecretion, as seen with Alcian blue. The neoplastic epithelial cells stained positive with cytokeratin and negative with vimentin and glial fibrillary acidic protein.

Follow-up

Postoperative recovery was uneventful. Ophthalmic and systemic evaluations, together with computed tomographic scans and magnetic resonance imaging, were performed at 6-week, 6-month, and 1-year follow-up examinations. There has been no evidence of local recurrences or dissemination.

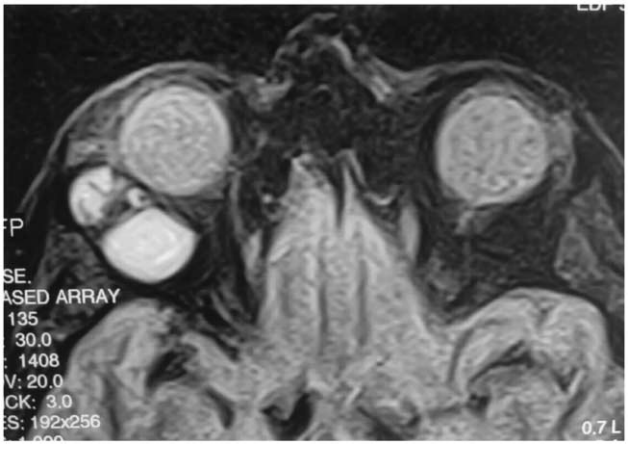

Figure 3. Magnetic resonance imaging shows a multicystic mass.

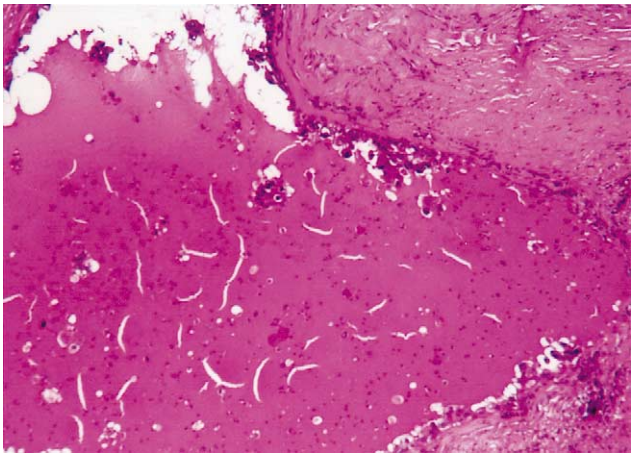

Figure 5. Low-power view of a cyst lined by cells with papillary arrangement and containing a proteinaceous exudate (stain, hematoxylin–eosin; original magnification, ×25).

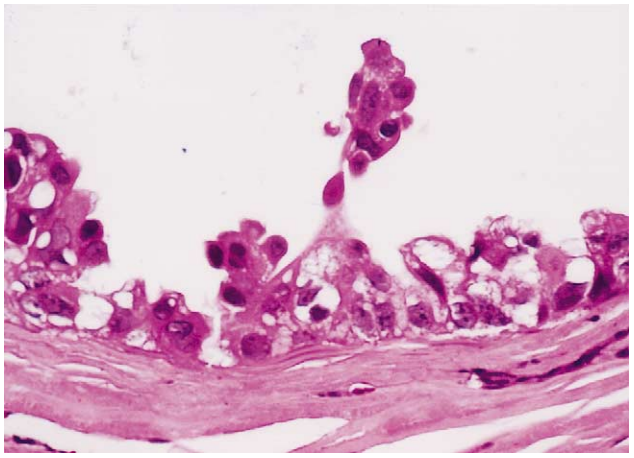

Figure 6. Papillary arrangement of neoplastic cuboidal cells (stain, hematoxylin–eosin; original magnification, ×250).

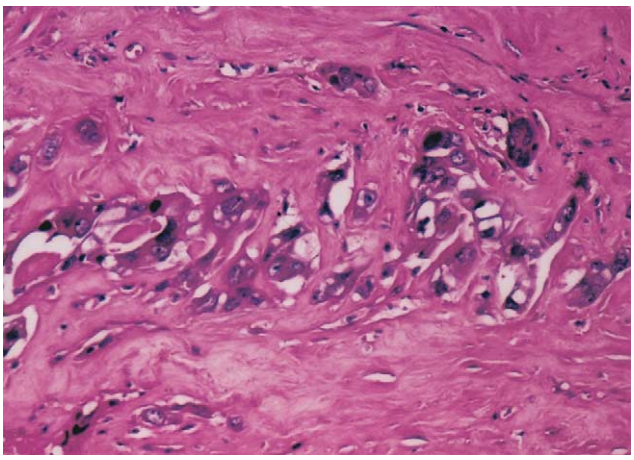

Figure 8. Infiltrating atypical large cells with a dense collagenous extracellular matrix (stain, hematoxylin–eosin; original magnification, ×125).

Discussion

Pathologic classifications of malignant epithelial tumors of the lacrimal gland include carcinoma in pleomorphic adenoma or adenocarcinoma ex-pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and others.[12,13] Wright et al[1] reported one of the largest series of primary malignant neoplasms of the lacrimal gland from one institution. The most frequent tumor was adenoid cystic carcinoma (38 [76%] of 50 cases), 6 (12%) were carcinomas arising in pleomorphic adenoma, and the remaining 6 (12%) were 4 adenocarcinomas, 1 squamous carcinoma, and 1 mucoepidermoid carcinoma. In the series of lacrimal gland tumors reported by Shields et al,[2] malignant tumors included adenocarcinoma ex-pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Font et al[14] reviewed their experience (which spanned a 23-year period) with 21 malignant epithelial tumors among 120 lacrimal gland masses. Twenty-one neoplasms were primary and three were metastatic lesions. The primary tumors included 12 adenoid cystic carcinomas, 2 de novo adenocarcinomas, and 7 malignant mixed tumors (carcinoma ex-pleomorphic adenoma). Recent series reported, in addition to the most frequent epithelial tumors, unusual subtypes of carcinomas and adenocarcinomas.[6,9] The latter group is formed by some entities brought from salivary gland tumors and includes acinic cell tumor,[3,4] clear cell epithelial–myoepithelial carcinoma,[5] polymorphous low-grade adenocarcinoma,[6] ductal adenocarcinoma,[7,8] adenocarcinoma with oncocytic features or oncocytic carcinoma,[9] spindle cell carcinoma,[6] basal cell carcinoma,[10] and adenocarcinoma not otherwise classified.

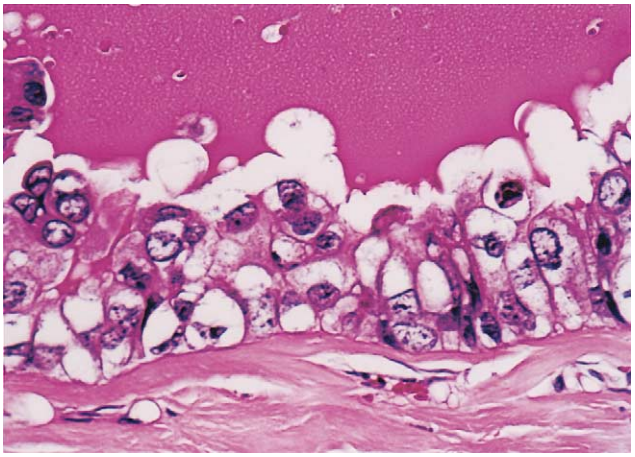

Figure 7. Focal area lined by larger epithelial cells with moderate nuclear pleomorphism and one mitotic figure. There was no evidence of mucin production by the tumor cells (stain, hematoxylin–eosin; original magnification, ×250).

This case represents a predominant cystic primary malignant epithelial tumor of the lacrimal gland composed of cuboidal and atypical epithelial cells with a focal papillary and desmoplastic infiltrative growth pattern and without mucous secretion. The term *cystadenocarcinoma* applied to salivary gland tumors has evolved from a descriptive manner used for a wide variety of tumors that exhibit cystic patterns of growth to a subset of distinct papillary and cystic malignant lesions that have an indolent biologic behavior. Foss et al,[11] in a review of 57 cases of salivary gland cystadenocarcinomas from the Armed Forces Institute of Pathology, used the following diagnostic criteria: (1) occurrence within a salivary gland, (2) invasive growth, (3) a predominantly cystic pattern of growth with or without a papillary component, and (4) the absence of acinar or mucoepidermoid differentiation or evidence of origin in a benign mixed tumor. Because the presence of cysts in salivary gland neoplasms is nonspecific, the differential diagnoses include acinic cell adenocarcinoma, low-grade mucoepidermoid carcinoma, and salivary duct carcinoma.

The patients with salivary gland cystadenocarcinoma ranged from 20 to 86 years of age; 71% were older than 50 years (Table 1). Both genders were equally affected, and the lesion was more common in whites. The most frequent symptom was painless swelling of the affected gland. Duration before consultation had a wide range from 1 month to 5 years, with an average of 14 months. Ninety percent of

Table 1. Summary of 57 Salivary Gland Cystadenocarcinomas*

Feature	Data
Age, yrs, mean (range)	58.8 (20–86)
Sex	No difference
Race	
White	93%
Black	7%
Location	
Major salivary gland	65%
Minor salivary gland	35%
Symptoms	Painless swelling
Duration before diagnosis	1 mo to 5 yrs; average 14 mos
Follow-up	
Local recurrences	7.5%
Lymph node metastasis	7.5%
Tumor free	
Alive	90%
Dead of other causes	10%

*Foss RD, Ellis GL, Auclair PL. Salivary gland cystadenocarcinomas. A clinicopathologic study of 57 cases. Am J Surg Pathol 1996;20:1440–7.

patients were alive without tumor with a mean follow-up of 59 months. Recurrences occurred in 3 of 40 patients and were not associated with cell type. Patients with recurrence were free of tumor an average of 93 months after treatment. Lymph node metastasis developed in 4 patients; 3 metastases were present at the time of diagnosis, and 1 developed 55 months after diagnosis from a tumor composed of large atypical cuboidal cells with a high mitotic rate. Three of these patients were alive and free of disease an average of 21 months after treatment of the metastasis; the other patient was lost to follow-up.

Although the cystic gross appearance and the presence of a papillary architecture are constant, three main cytomorphologic types have been described (Table 2). The most frequent is a neoplastic epithelium composed of uniform, small cuboidal cells with hyperchromatic nuclei and a low

Table 2. Pathologic Findings of Salivary Gland Cystadenocarcinomas*

Finding	Data
Size, cm, mean (range)	2.3 (0.4–6.0)
Gross appearance	Cystic or multicystic
Light microscopy	Infiltrative growth with desmoplastic response
Arrangement	
Papillary	75%
Solid foci	28%
Cytomorphology	
Small cuboidal cells	61%; 0–1 mitotic figures per 10 HPF
Large cuboidal cells	16%; 1–5 mitotic figures per 10 HPF
Columnar cells	12%; up to 30 mitotic figures per 10 HPF
Mixed	5.5%
Other cells	<5% (mucous, clear, or squamous cells)
Extracellular mucin	75%
Perineural invasion	9%
Vascular invasion	2%

HPF = high-power field.
*Foss RD, Ellis GL, Auclair PL. Salivary gland cystadenocarcinomas. A clinicopathologic study of 57 cases. Am J Surg Pathol 1996;20:1440–7.

Table 3. Histologic Grading of Salivary Gland Neoplasms and Their Lacrimal Gland Counterpart

Salivary Gland	Lacrimal Gland
Low-grade malignancies	
Acinic cell carcinoma	Acinic cell carcinoma[3,4]
Mucoepidermoid carcinoma (grade I or II)*	Mucoepidermoid carcinoma
Cystadenocarcinoma	Idem†
Basal cell adenocarcinoma	Basal cell adenocarcinoma[9]
Polymorphous low-grade adenocarcinoma	Idem[6]
Epithelial–myoepithelial carcinoma	Clear cell epithelial–myoepithelial carcinoma[5]
High-grade malignancies	
Mucoepidermoid carcinoma (grade III)*	
Adenocarcinoma poorly differentiated	Adenocarcinoma de novo (NOS)
Squamous cell carcinoma	Idem[1]
Carcinoma in pleomorphic adenoma	Idem
Adenoid cystic carcinoma	Idem
Salivary duct carcinoma	Ductal adenocarcinoma[7–8]

*Grades I, II, and III refer to increased predominance of the squamous component.
†This report.
NOS = not otherwise specified.

mitotic rate. Less often, the cuboidal cells are larger and have abundant eosinophilic cytoplasm, centrally located irregular nuclei with coarse chromatin, prominent nucleoli, and 1 to 5 mitotic figures per 10 high-power fields. Rarely, columnar cells resembling enteric epithelium, with moderate atypia and numerous mitotic figures, line the cysts. The second type is not necessarily associated with a more aggressive behavior than tumors composed of small cuboidal cells. Tumors in which columnar cells are preponderant have an increased metastatic potential.[11]

In an attempt to determine the most effective treatment of adenocarcinomas of the lacrimal gland, Heaps et al[15] reviewed 13 cases of primary adenocarcinoma of the lacrimal gland (de novo) referred from several eye centers. Half of the patients died of metastatic disease, 3 were alive with recurrence, and 4 were alive and disease free. On the basis of this retrospective, multicentric, noncomparative, uncontrolled study of case series, the authors suggested that therapy should include exenteration and radiotherapy soon after diagnosis. A shorter duration of symptoms was associated with a better prognosis. Wright et al[1] mentioned that tumor histopathology was the most significant factor in the survival of patients in their series. However, their results were based on a few cases without further histologic classification beyond the diagnosis of adenocarcinoma. Among tumors of the salivary glands, various types are distinguished for purposes of recognition, prognosis, and treatment.[16] Malignant salivary gland tumors are divided histologically into low-grade and high-grade malignancies. The review of reported cases of malignant epithelial tumors of the lacrimal gland diagnosed according to the tentative World Health Organization classification of salivary gland tumors (Table 3)[16] suggests that the biologic behavior, treatment, and

prognosis based on the subtypes of primary lacrimal gland carcinomas are warranted.

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