Primary Undifferentiated Large Cell Carcinoma of the Lacrimal Gland

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Purpose: To report a unique case of primary undifferentiated large cell carcinoma (LCCA) of the lacrimal gland, a tumor not previously described in the ophthalmic literature.

Design: Single interventional case report.

Participants: A patient affected by undifferentiated LCCA of the lacrimal gland.

Methods: A 65-year-old white man with a 3-month history of a painful mass in the left lacrimal gland fossa underwent an incisional biopsy that revealed a "high-grade" epithelial malignancy. Systemic workup revealed enlargement of the regional lymph nodes, and subsequently the patient underwent extended exenteration with clear histologic margins and radical neck lymphadenectomy followed by adjunctive radiotherapy. Fifteen months postoperatively, the patient is alive and well without evidence of local recurrence or metastatic disease.

Main Outcome Measures: Treatment result, evidence of local recurrences or distant metastasis, and follow-up.

Results: Histologic examination revealed a poorly circumscribed tumor composed of large cells invading orbital fat, lateral rectus muscle, and peripheral nerves. The surrounding orbital bone was infiltrated, but the surgical margins were clear. The cell population was composed of large cells (>30 μm) with eosinophilic cytoplasm and ovoid and irregular nuclei containing a prominent nucleoli and coarse chromatin. The cell borders were well defined. Mitosis figures were abundant, and Ki-67 was positive in more than 60% of the cells. The cells were arranged in cords and trabeculae or irregular sheets of discohesive cells. The immunophenotype analysis showed positivity for cytokeratin but negative cytokeratin 20 stains, which is considered a distinctive feature of LCCA.

Conclusions: Undifferentiated LCCAs are rare tumors of the major salivary glands, especially the parotid gland. Primary undifferentiated LCCA of the lacrimal gland has never been reported in the literature. Differential diagnosis must include a primary source in another organ. Given the aggressive nature of the tumor, radical surgery followed by radiotherapy is recommended, but evidence-based indications regarding the preferred line of treatment are lacking and the prognosis remains guarded.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2011;118:1189–1192 © 2011 by the American Academy of Ophthalmology.*

Primary undifferentiated carcinomas of the salivary glands are rare tumors that predominantly affect the parotid, where they represent 1% to 11.4% of all the malignant tumors in this location.[1,2] Of 43 cases of salivary undifferentiated carcinomas reported in the last 30 years, 42 occurred in the parotid gland.[1] Historically, undifferentiated carcinomas of the salivary glands have evolved into the following specific subtypes: small cell carcinoma (SMCCA), large cell carcinoma (LCCA), and lymphoepithelial carcinoma. The last 2 malignancies have a morphology similar to epithelial cells, except for the lack of evident lymphocytic infiltration among the neoplastic epithelial cells in LCCA.[3] The small cell type is more common (66.7%) in comparison with the large cell type (33.3%).[1] Most SMCCAs and some cases of LCCA express neuroendocrine markers.[4,5] These subtypes of undifferentiated carcinomas have been included in the most recent World Health Organization classification of tumors of the salivary glands as 2 distinct entities: SMCCA and LCCA.[4,5] Patients with LCCA usually have a history of a painful, rapidly growing, firm mass adherent to adjacent tissues. Distinctive histopathologic features of primary undifferentiated LCCA are cell size >30 μm, a Ki-67 labeling index >50%, and negative immunoreactivity for cytokeratin 20 (CK20).[4] In the parotid gland, LCCA rarely displays neuroendocrine differentiation, and in this form it is classified as a different entity under the name "large cell neuroendocrine carcinoma."[6,7] The prognosis is generally poor, and tumor size and TNM (tumor, nodes, and metastasis) staging seem to be the most important factors affecting the survival, with a fatal outcome in patients with tumors >4 to 6 cm.[8,9]

Until now, LCCA has not been included in the most updated classifications of the lacrimal gland tumors.[10,11] To the best of our knowledge, we describe the first example of primary undifferentiated LCCA of the lacrimal gland, in-

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2010.10.039

cluding clinical, histopathologic, and immunohistochemical features of this rare high-grade malignancy.

Case Report

A 65-year-old white man was referred to the senior author's department with a 3-month history of progressive, painful left lacrimal gland enlargement. His medical history was positive for cigarette smoking, but negative for neoplasia, medications, and significant medical conditions. Ophthalmic plastic examination revealed 2 mm of proptosis, a mild elevation and abduction deficit, and 3 mm of ptosis in the left side (Fig 1, available at http://aaojournal.org.). A firm, tender mass was palpable in the superotemporal quadrant of the left orbit. Visual acuity was 20/20, and intraocular pressure was 18 mmHg in both eyes. Pupillary, slit-lamp, and funduscopic examinations were unremarkable. Axial and coronal computed tomography showed a nonhomogeneous, irregularly shaped, extraconal mass located in the left lacrimal fossa with signs of bone erosion and infiltration of the lateral rectus muscle (Fig 2, available at http://aaojournal.org.). Orbital magnetic resonance imaging revealed a hyperintense, irregular lesion infiltrating the lateral and the superior recti muscles (Fig 3, available at http://aaojournal.org.). The patient underwent lacrimal gland biopsy, which disclosed a "high-grade" malignancy, and at this stage differential diagnosis included metastatic disease, primary epithelial malignancies, and orbital lymphoma. A systemic workup, including total body computed tomography and positron emission tomography, ruled out primary malignancies elsewhere, but revealed the involvement of the regional neck lymph nodes. An extended lid-sparing exenteration was performed by one of the authors (FPB), and a concomitant left radical neck lymphadenectomy disclosed the positivity of 14 of 21 lymph nodes. Final TNM classification for this patient was $T_{3A}N_1G_3$. A large dermis fat graft covered by the residual eyelid flaps was used to protect the exenterated orbit. Adjunctive radiotherapy was administered postoperatively to both surgical sites, and the patient has been closely monitored every 4 months since. At the time of the report, 15 months postoperatively, the patient showed no evidence of local recurrences or distant metastasis (Fig 4, available at http://aaojournal.org.). This study was approved by the institutional review board/ethics committee, and the authors have no financial interest or financial support.

Pathologic Findings

Gross examination revealed a poorly circumscribed, whitish solid mass, measuring 20×15 mm, separated from the eye globe but attached to the surrounding bone. Microscopic examination revealed that the mass was infiltrating fat, muscle, bone, and peripheral nerves, but the surgical margins were clear of the tumor. There was no residual normal lacrimal gland tissue in the histologic specimen evaluated. The tumor was composed of large polygonal or round cells (>30 μm) with well-defined eosinophilic cytoplasm and ovoid nuclei containing prominent nucleoli and coarse chromatin. The cells were arranged in cords, and trabeculae or irregular sheets of discohesive cells with frequent mitotic figures and apoptotic cells were numerous (Fig 5, available at http://aaojournal.org.). There was no evidence of ductular or squamous differentiation. A mild and patchy infiltrate of lymphocytes with a few lymphoid follicles was observed. Periodic acid-Schiff and alcian blue stains failed to demonstrate any intracellular or extracellular mucin. The labeling index of Ki-67–positive cells varied from 40% to 60% in different areas. The tumor cells were strongly positive for pan cytokeratin (AE1/AE3) and CK-7, and negative for CK-20 (Fig 6). No immunoreactivity for neuroendocrine markers (chromogranin and synaptophysin), S-100 protein, or p-53 was found, and the immunoreactivity for HMB-45 and Melan-A/MART-1 was negative. On the basis of these features, the diagnosis of primary undifferentiated LCCA was established first by a general pathologist (RB) and independently confirmed by an ophthalmic pathologist (JOC).

Discussion

The diagnosis and management of malignant epithelial lacrimal gland tumors are based on the recent knowledge that they are histologically similar to and clinically behave like the more common counterparts of the major salivary glands. The most updated classification of lacrimal gland tumors has been recently modified on the basis of the World Health Organization classification of salivary gland tumors.[4]

Undifferentiated carcinomas are rare high-grade malignant tumors of the salivary glands characterized by the absence of features of other specific tumor types. We were unable to find a "primary large cell carcinoma of the lacrimal gland" in Medline using the following search strategy: ("lacrimal apparatus" OR "lacrimal gland") AND ("carcinoma, large cell" OR "large cell carcinoma"). In one of the largest series of epithelial lacrimal gland tumors published before the current knowledge of subtypes, Ni et al[12] listed 20 of 127 malignant epithelial tumors as being undifferentiated carcinomas. More recently, Weis et al,[13] in a series of 118 epithelial tumors of the lacrimal gland, reclassified 2 cases as "unclassifiable carcinomas," which may have represented undifferentiated carcinomas. Although the authors did not provide any images of these 2 cases, the microscopic description of the first case is similar to the findings observed in SMCCA of the salivary gland, including poorly differentiated adenoid cystic carcinoma in the differential diagnosis.[1] The second tumor was composed of eosinophilic epithelioid cells with a high mitotic rate and no evidence of mucin suggestive of LCCA.

The most important differential diagnosis is metastatic disease, poorly differentiated carcinomas, adenocarcinoma of the lacrimal gland, malignant melanoma, and anaplastic lymphoma.[14,15] Large cell carcinoma should not be confused with adenocarcinoma not otherwise specified, a malignant tumor with ductular differentiation that lacks any other characteristic representative of other types of lacrimal gland tumors.[16] Carcinoma ex pleomorphic adenomas may show predominant or mixed features of adenocarcinoma, adenoid cystic carcinoma, poorly differentiated carcinoma, and even undifferentiated carcinoma. A clinical history of a long-standing mass, history of an excised pleomorphic adenoma, and histologic evidence of a benign pleomorphic adenoma support this diagnosis. Metastasis to the lacrimal gland is rare, representing 7% of all lacrimal fossa masses in one study,[17] and may initially present as a lacrimal gland tumor without history of primary tumor.[18] Clinical examination, light microscopy, and immunohistochemistry are helpful to differentiate LCCA from other poorly differenti-

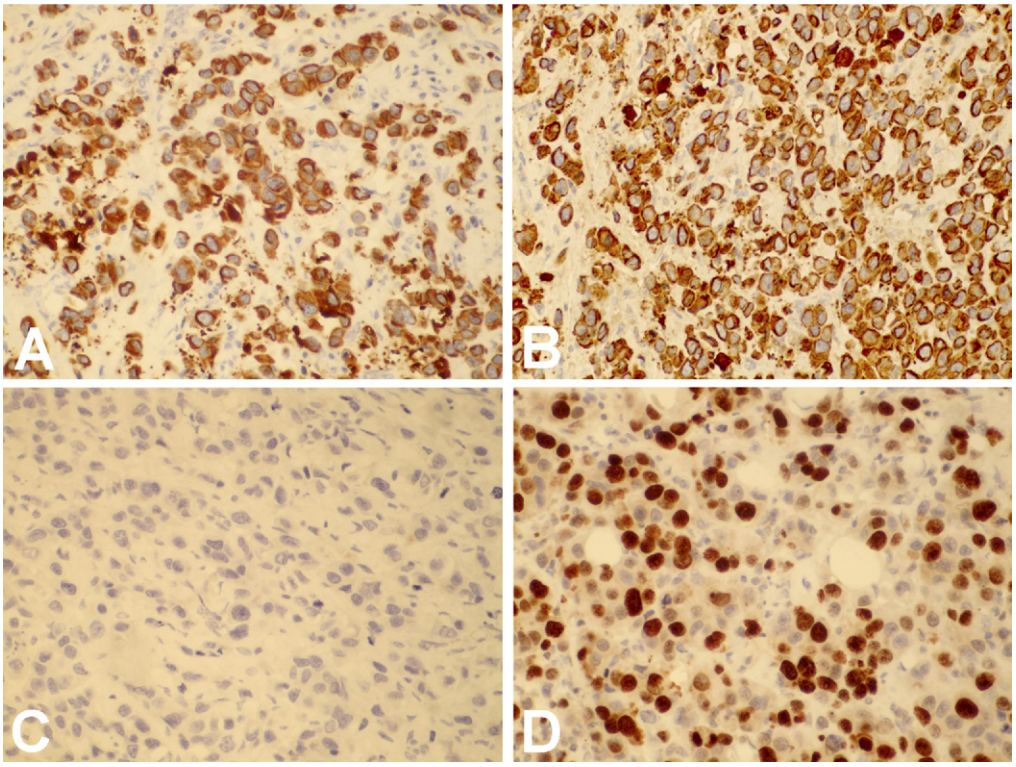

Figure 6. Immunohistochemical findings. **A,** Tumor cells are positive for AE1/A3 cytokeratin antibody (×400). **B,** Strong positive staining for CK-7 (×400). **C,** Tumor cells are negative for CK-20 (×400). **D,** Most of the tumor cell nuclei are positive for proliferative marker Ki-67 antibody (×400).

ated or undifferentiated metastatic tumors.[19] The case reported in this article fulfills the criteria for the diagnosis of undifferentiated LCCA clinically and histologically.[4]

The management of lacrimal gland LCCA is especially challenging because our knowledge of its clinical features, behavior, and prognosis needs to be derived from its counterparts of the salivary glands, especially the parotid gland, where it represents approximately 1% of epithelial salivary gland neoplasms.[9] In the salivary glands, LCCA shows an aggressive behavior, with rapid growth, infiltration of surrounding tissues, and regional lymph nodes metastasis.[9] Facial nerve palsy and cervical lymph node enlargement are common presenting signs of parotid gland LCCA.[9,20] The treatment of choice is complete excision, lymph node dissection, and adjuvant radiotherapy. Only 3 of 12 patients described in one series remained alive 17 months, 19 months, and 15 years after treatment.[9] The overall survival rate at 5 years is 0% to 36%, whereas patients with tumors >6 cm have a 100% mortality rate.[8,9] Although there is no consensus regarding the role of chemotherapy to prevent lymph node recurrence or distant metastasis, its use might be of value when the tumor exceeds 4 cm.[2]

In conclusion, in the current case, exenteration with free margins, lymph node dissection, and postoperative radiotherapy were performed, followed by close patient observation. Because primary undifferentiated LCCA has never been described in the lacrimal gland, a definitive assessment of suitable treatment and prognosis is difficult at this time.

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Footnotes and Financial Disclosures

Originally received: April 3, 2010.
Final revision: October 25, 2010.
Accepted: October 25, 2010.
Available online: January 26, 2011. Manuscript no. 2010-493.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

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