Adenoid cystic carcinoma of the lacrimal gland masquerading as dacryoadenitis

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Abstract
Adenoid cystic carcinoma (ACC) of the lacrimal gland is a rare, life-threatening tumor often not diagnosed until advanced stages. This malignancy usually presents with nonspecific symptoms such as periocular pain and non-axial proptosis. We present a case of a 40-year-old female experiencing these symptoms, whose initial lacrimal gland biopsy was consistent with chronic dacryoadenitis. Reappearance and worsening of her symptoms after treatment led to a total dacryoadenectomy, which confirmed the presence of ACC. Close follow up of the clinical signs and imaging in this patient allowed us to suspect and finally diagnose an invasive malignancy that was masquerading as a chronic dacryoadenitis.

Key words: Lacrimal gland; adenoid cystic carcinoma; dacryoadenitis; inflammation; orbital neoplasm.

Introduction
Lacrimal gland tumors are rare, yet potentially lethal when an epithelial malignancy is involved. Adenoid cystic carcinoma (ACC) is the most common malignant tumor, accounting for about 20% of all epithelial tumors and 65% of all malignant epithelial tumors of the lacrimal gland. Classically presenting with a short clinical history (less than 12 months) involving non-axial proptosis, pain, and lacrimal nerve paresthesia. It has no gender preference and tends to affect young individuals in the fourth decade of life. In spite of aggressive treatment, ACC has a high recurrence rate, often extending into neighboring tissues, leading to only 19% 10 year survival (median overall survival is 7.6 years). Unfortunately, ACC diagnosis is challenging, since it does not always have the classic presentation and can emulate other diseases. Therefore, a high index of suspicion for malignant processes should always be taken into account to avoid delay in diagnosis and treatment that could prevent potential tumor spread to neighboring tissues and/or metastases.

We present a case of a young female with known autoimmune systemic disease, who presented with clinical signs suggestive of a chronic dacryoadenitis, confirmed by an excisional biopsy. Due to her unusual clinical course and lack of steroid response, she underwent a diagnostic dacryoadenectomy, which confirmed the presence of an unexpected adenoid cystic carcinoma.

Case Report
A 40-year-old African-American female with history of fibromyalgia, migraines, and asthma, presented with 10-month history of increasing right periorcular pain (3/10) and superotemporal orbital tenderness. Clinical examination revealed 3mm non-axial right exophthalmos and mild pain with palpation of the right superotemporal orbit. Trigeminal sensation was preserved and the rest of the exam was within normal limits. A head and orbit...
computed tomography (CT) was performed, showing a well-defined, moderately enlarged, homogeneous right lacrimal gland, without signs of calcification, bony erosion or expansion of the lacrimal gland fossa (Figure 1A). Due to the broad differential diagnosis, an excisional biopsy via a right anterior orbitotomy through the skin crease incision was performed. A 1.5x0.5x0.2cm specimen of the lacrimal gland was removed, and pathology showed multiple small interstitial foci of lymphocytes and plasma cells, consistent with chronic dacryoadenitis (Figure 2A). There was no evidence of malignancy in any part of the specimen.

Given these findings, the patient was started on a course of oral steroids, with poor tolerance. She was then given IV pulse methylprednisolone (1g/day x 2 times), which lead to pain improvement to 1/10 and resolution of her proptosis. However, after one month of apparent symptom relief, both the pain and proptosis recurred. At this point, her rheumatologist advised further increase of immunosuppressive treatment.

Because there was a noticeable change in the nature of her pain, which increased to 8/10, progressing to constant, and was interfering with activities of daily living, as well as a new non-axial 4mm proptosis with a palpable, hard right lacrimal gland, a new CT scan was requested. The imaging demonstrated significant enlargement of the right lacrimal gland, when compared with the previous CT. This structure was well-defined, but non-homogeneous in appearance, and abutted the temporal aspect of the right globe. In addition, there were new irregular bony erosions in the orbital side of the greater wing of the sphenoid (Figure 1B). These findings were concerning for a malignant process, and a total dacryoadenectomy was completed, which confirmed the presence of an ACC. Since the bone was macroscopically eroded, a lacrimal gland fossa en-bloc excision was also included. Histopathology showed a grade 3 poorly differentiated ACC, predominantly solid type, measuring 2.5cm in its greatest dimension, and extending to the edges of the specimen (Figure 2B). The frontal bone was also invaded with perineural and intraneural spread (Figure 2C). Staging, including positron emission tomography-CT (PET-CT) showed only localized disease and she was classified as T4b N0 M0 (Tumor size, Nodal status, and Metastasis) since the tumor had invaded bone, but had not spread to lymph nodes or metastasized.

Treatment options and prognosis were discussed with the patient, who elected to receive radiotherapy (RT) and chemotherapy. A total dose of 76 Gy of a combination of photon and proton radiation therapy was administered in 38 fractions. Concurrent with RT, patient received 40mg/m² intravenous adjuvant cisplatin weekly for 6 weeks as radiation sensitizer. After 6 months, patient is asymptomatic without any signs of disease recurrence.

**Discussion**

Adenoid cystic carcinoma (ACC) of the lacrimal gland is a rare epithelial malignancy, with an incidence of 0.11 cases per million per year.6 African-Americans represent 18.1% of all ACC cases in the United States, and tend to have poorer prognosis compared to Caucasians.4,7 ACC has no gender predilection and can occur at all ages, with a median age between 40-50 years.6,8 The most common differential for lacrimal ACC include lymphoma, which tends to present in patients greater than 60 years of age and can have bilateral involvement; and pleomorphic adenoma, which has a slower progression and is usually painless.3 The characteristic painful nature of ACC is related to its tendency for perineural invasion, which was present in this case and occurs in 16.7% to 72% of patients depending on the series.3,8 On CT imaging this malignancy often appears nodular with irregular margins and bone destruction, in contrast to the initial presentation of our patient, who had a homogenous smooth lesion without bone involvement.

Our patient’s TNM classification relates to a poor prognosis. T3 or T4 tumors represent masses of 2.5cm or larger that have a significantly higher chance of local recurrence and distant metastases as well as decreased survival. In addition, the predominance of basaloid cells (solid type), as seen in this case, is associated with a significant reduction in disease-free survival.10

**Figure 2.** A. Initial excisional biopsy of the right lacrimal gland showing chronic dacryoadenitis with small interstitial foci of lymphocytes and plasma cells (closed arrow heads). Lacrimal ducts are surrounded by benign fibroadipose tissue and no malignancy is noted in any part of the specimen (H&E stain, x40 magnification). B. Subsequent right dacryoadenectomy showing small myoepithelial cells arranged in predominantly solid nests with few pseudoglandular lumina representing the malignancy, which is surrounded by reactive stroma. The tumor is seen throughout the surgical specimen and extends to the black-inked margin (arrow ) (H&E stain, x40 magnification). C. Bone specimen after the en-block excision of the right lacrimal gland fossa, showing intrasosseous adenoid cystic carcinoma with intraneural invasion (open arrow heads ). Nerve is surrounded by benign fibroconnective tissue and viable bone (H&E stain, x100 magnification).
En bloc excision is advocated for small well-circumscribed malignant lesions, like our case. Aiming to increase survival and decrease recurrence, the goal of surgical treatment is to obtain clear margins, which was not possible in this case because the tumor had already developed perineural invasion. Radical surgery should be considered for extensive disease, but orbital exenteration to decrease local or regional recurrence has not been shown to change overall survival. No studies have been published on systemic chemotherapy or radiation therapy for lacrimal ACC, likely due to its rare nature. Instead, treatment data for advanced lacrimal ACC has been extrapolated from studies of more common, but still morphologically and embryologically similar, ACCs of the head and neck. Surgical resection followed by radiation therapy is considered the standard of care for locally advanced tumors such as our patient’s, and adjuvant cisplatin can be added for patients with high risk of recurrence. Studies have shown that postoperative radiation therapy leads to a significant increase in locoregional control and five year disease free survival when compared with surgery alone. Although our patient presented post-operative chemoradiation therapy with curative intent, her follow up is still in process.

Local recurrence in the orbit or skull base usually occurs within 2.2 years and is expected in 67% of patients treated with globe-preserving surgery. It is closely associated with perineural spread, therefore can be extremely painful. If our patient presents with recurrence, aggressive local resection should and will be considered in attempt to eradicate any apparent tumor. Orbital exenteration is indicated in case of symptomatic intraconal recurrence, and bone removal should take place if there is evidence of bone involvement. This patient has a high risk for intracranial spread; if complete resection is not possible, palliative surgery to remove part of the tumor can be considered for symptomatic control. This patient is also at high risk of metastatic disease, and in this instance chemotherapy with cisplatin (100mg/m2 1-6 cycles) and etoposide (30mg/m2 8 cycles), although only marginally effective, seem to be the most indicated course of treatment. A series of 20 cases of lacrimal ACC in the US found that 80% developed metastasis with the most commonly affected sites being lung, bone, liver and neck lymph nodes, kidney, and brain. The median survival with metastatic disease was only 8 months. This is a major concern in our patient, and therefore close follow-up with clinical examination, MRI, and PET-CT imaging are indicated.

In summary, the management of lacrimal gland ACC is challenging, because the disease is often advanced at time of diagnosis. We believe this patient likely had the malignant tumor when she first presented, but the excisional biopsy was not able to encounter the ACC. The inflammatory microenvironment of this first specimen, compatible with chronic dacryoadenitis, might actually be representative of a local immune response caused by inflammatory proteins secreted in the tumor microenvironment. It is well established that inflammation can lead to cancer, but even malignancies that are not triggered by inflammation tend to be surrounded by inflammatory cells and inflammatory mediators. The interaction between tumor cells and the inflammatory microenvironment increases the migration, invasion and survival of malignant cells.

We have found no previous published cases of ACC of the lacrimal gland masquerading as dacryoadenitis, and advocate that patients with diagnosis of dacryoadenitis be followed-up closely. A high index of suspicion for malignancy is required if symptoms persist and/or change, and dacryoadenectomy may be urged to diagnose ACC in its early stages.