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Case Report

Metachronous Bilateral Adenoid Cystic Carcinoma of the Lacrimal Gland

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Abstract

Background: To report an aggressive and treatment-resistant adenoid cystic carcinoma (ACC) of the lacrimal gland (LG).

Case report: A 29-year-old woman with diagnosis of LG-ACC had operations 7 times, radiotherapy 3 times and systemic chemotherapy 2 times. Although she generally responded therapies, the duration of remissions was short lived and the tumor progressed locally and did hematogen metastases.

Conclusion: LG-ACC presents a therapeutic challenge despite its slow growth rate and lower likelihood of lymph-node metastasis. Postoperative radiotherapy with wide margins should be utilized —even after a complete resection— because of persistent recurrences, perineural invasion and hematogenous spread.

Keywords: Adenoid cystic carcinoma, lacrimal gland, radiotherapy

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Competing Interests: The authors have declared that no competing interests exist.

Consent: We confirm that family members of the patients have given their informed consents for the case report to be published.

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Introduction

ACC encompasses %13.4 of LG tumors and consists of epithelial and myoepithelial cells with several morphological configurations [1, 2]. In spite of slow growth rate, persistent local recurrences and late distant metastases occur frequently. It often originates from parotid and submandibular glands and in rare instances, from the lacrimal gland [2, 3]. Stage>T3, perineural invasion, a positive surgical margin, basaloid subtype, metastasis and recurrence are primary factors that adversely affect prognosis [4, 5]. The disease-specific and overall survival rates at 10-year follow-up were given as %51.4 and %38.7 respectively [1]. Metastasis can occur one-third of patients, with lung, liver, brain and bone being the most common metastasis sites [4]. The primary therapeutic approach for ACC is surgery of the lacrimal gland; however, aggressive surgery and enucleation do not improve survival [4, 5]. The addition of adjuvant radiotherapy to surgery significantly improves local control rates [2-4]. Chemotherapy is generally used in recurrent or inoperable cases [2].

Here, we discuss the role, effectiveness and relevance of multi-modality therapy in a patient with metachronous ACC, which developed in bilateral lacrimal glands in three years intervals.

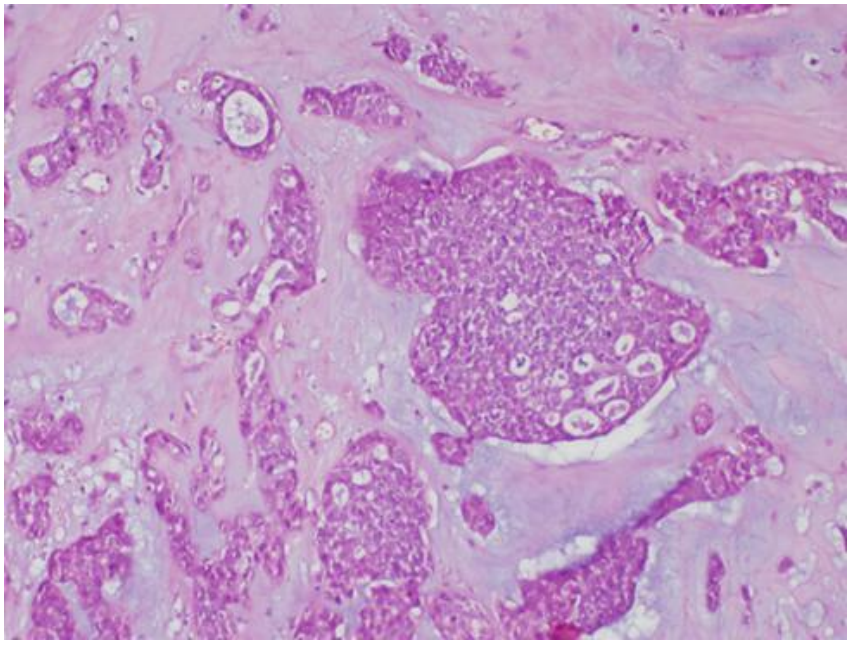

Figure 1 Adenoid cystic carcinoma of LG. Tumoral infiltration of solid, cribriform and tubular pattern are observed (H & E, X100)

Case summary

A 29-year-old woman who had a normal delivery 2 months ago presented to a University Ophthalmology Clinic with an anterior and medial protrusion of the left eye. She was diagnosed with biphasic (epithelial and myoepithelial) tumor by a fine-needle aspiration biopsy (FNAB) performed in March 2009. On magnetic resonance imaging (MRI) of the orbit, a mass lesion (4x3x3.2 cm) with non-homogenous contrast enhancement was detected at the left lacrimal gland, which invaded the lateral wall of the left orbit and had intermediate signal intensity on T1-weighted images and a hyper-intense signal on T2-weighted images. Chest and whole abdominal computed

tomography scanning with contrast showed no systemic metastases. In May 2009, the patient underwent mass excision and bone curettage in another University Hospital. Histopathological evaluation revealed basaloid subtype of ACC with invasion of frontal bone (Figure 1). Immunohistochemical studies with keratin and smooth muscle actin (SMA) shoved intrastoplasmic positivity. On the restaging MRI following surgery, a residue (4x3x1 cm) was seen in the left retro-orbital adipose tissue at the vicinity of the lateral rectus muscle; as a result, re-excision was performed in June 2009. Again, a strip-like residual tissue (3x3x0.3 cm) was observed on the follow-up MRI after re-excision. Then, fractionated stereotactic radiotherapy (FSRT) was given to the left lacrimal gland and frontal region by using CyberKnife Robotic Radiosurgery system (Accuray, Sunnyvale, California) in June 2009. FSRT was delivered with 24 Gy in 3 fractions to %72 isodose (Figure 2). No complication other than Grade I conjunctivitis was observed during therapy. On the follow-up MRI and computed tomography (CT) scan after FSRT, we observed a complete response (Figure 3). Follow-up was scheduled for 3-month intervals.

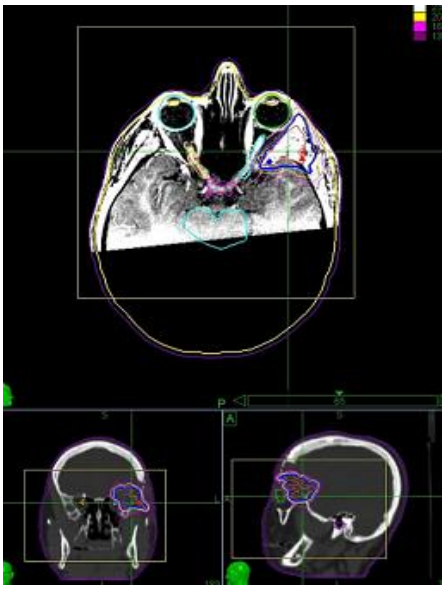

Figure 2 CyberKnife plan.

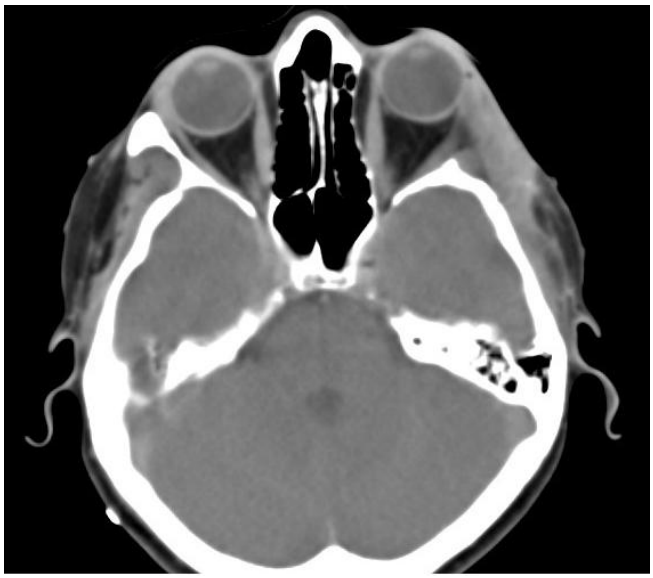

Figure 3 The CT scan with contrast enhancement shows that the masses in the left LG were totally cured.

On the follow-up MRI in March 2010, recurrence (1.8x1.2x1.0 cm) was evident in the zygomatic bone corresponding to the inferior region of the left orbit. In addition, metastases were evident in the left frontal bone (2.0x1.2 cm), in the inner tabula adjacent to the sylvian fissure (7x7 mm) and in the middle left region of the cranial fossa (1.3x1.2 cm) (Figure 4). Metastasis at the frontal bone was excised in April 2010. Histopathological evaluation was reported as frontal bone invasion by ACC. The patient received 6 sessions of a chemotherapy regimen in 28-day intervals, consisting of cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2) and cisplatin (50 mg/m^2). The postoperative clinicopathological evaluation was considered to be stable disease. Unfortunately, disease progression in the middle left region of the cranial fossa and inner tabula adjacent to the sylvian fissure was detected in a follow-up visit in November 2010. Tumor excision via a left petrous craniotomy in the frontal lobe was performed for the fourth time, and the defect was repaired using titanium plates. Histopathological evaluation was reported as ACC. Between

December 2010 and January 2011, image-guided intensity-modulated radiotherapy (IG-IMRT) via Tomotherapy using 2 Gy daily fractions up to 60 Gy at 2 phases was delivered to all metastatic lesions and osseous involvement sites (Figure 5). Dose was limited to 50 Gy in areas that previously received radiotherapy by stereotactic surgery. No complication other than Grade II conjunctivitis was observed. The follow-up MRI after radiotherapy detected that lesions at the middle cranial fossa and the sylvian fissure, which were observed on previous imaging studies, disappeared completely; however, bone metastases persisted. Follow-up was scheduled for 3-month intervals.

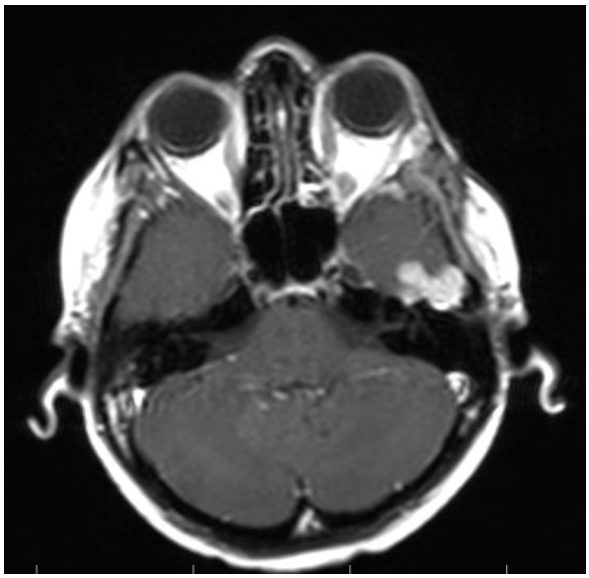

Figure 4 T1 weighted MRI with contrast shows that there is new metastatic lesion in the middle left region of the cranial fossa

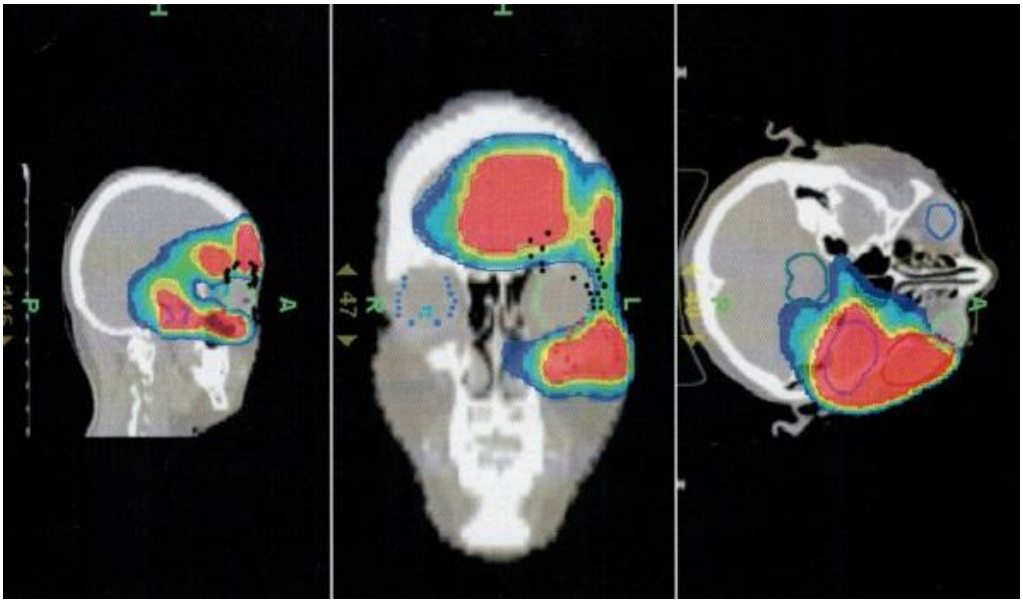

Figure 5 Sagittal, coronal and axial images of Tomotherapy planning shows the first Tomotherapy irradiation volumes of metastatic areas.

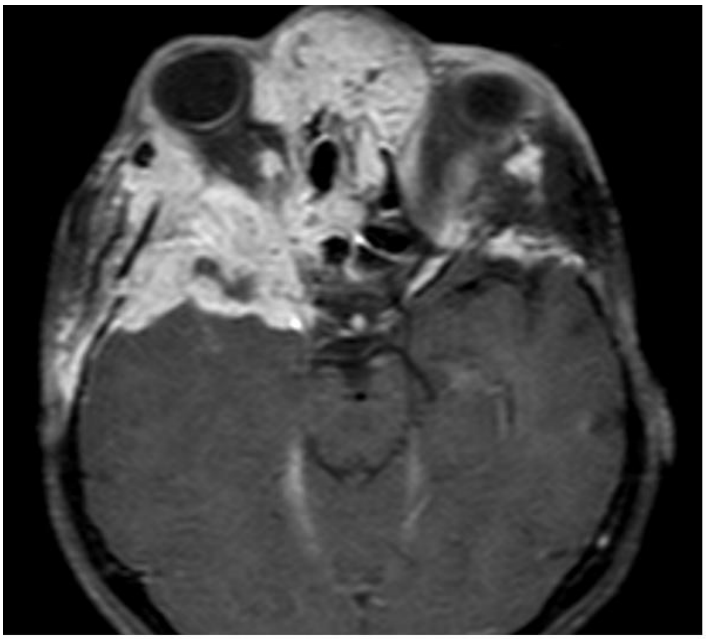

Figure 6 T1 weighted MRI with contrast shows that there were rapid progression of lesions in ethmoid sinus area and new formation of tumoral mass at lateral wall of the right orbit that leads expansion towards to the right temporal region

On follow-up MRI in September 2011, marked progression was observed in the mass lesion at the inferolateral wall of the left orbit and right half of the frontal sinus. The tumor was excised from the frontal region via partial maxillectomy in October 2011. Histopathological evaluation was reported as persistent ACC at soft tissues and osseous tissue. After surgery, the patient received 6 sessions of paclitaxel (75 mg/m^2). Under the paclitaxel chemotherapy, there were rapid progression of lesions in ethmoid sinus area and new formation of tumoral mass at lateral wall of the right orbit that leads expansion towards to the right temporal region. This new mass lesion originating from the contralateral lacrimal gland was excised. Histopathological evaluation was reported as ACC. Because of clinical and radiological progression and the onset of severe pain, IG-IMRT was delivered with 46 Gy in 2 Gy fractions (5 fractions per week) to all metastatic lesions and osseous involvement sites using tomotherapy between May and June 2012. IG-IMRT provided sufficient pain control, but the patient died in December 2012 due to disease progression.

Discussion

An epidemiologic study from the 'Surveillance Epidemiology and End Results database' by Andreoli et al, shows that lymphoma (%58), ACC (%13.4), adenocarcinoma (%3.8) and mucoepidermoid carcinoma (%3.6) accounted for most LG tumors [1]. ACC is usually seen in women ages 35-45 and involves the left LG more frequently [1-3]. In a study by Weis et al., ACC was reported in %29 to %64 of all malignant lacrimal gland tumors [8]. In a study by Chawla et al. involving 66 cases, the most common malignant type was ACC with a frequency of %75; a median age of 32 years and the left side as the most common area of localization [3]. The majority of patients present with complaints of proptosis, ptosis, pain and diplopia. At diagnosis, there is a

palpable mass at the lateral margin of orbit in %50 of patients, preoperative pain in %9 and bone erosion in %50 [1-3]. CT and MRI are helpful in identifying osseous invasion and tumor spread to adjacent organs. In our case, the patient presented to us with proptosis. She also experienced severe pain as the disease progressed and as a second primary LG developed. CT and MRI were used in diagnosis and follow-up.

Complex anatomy of the orbit and aggressive bone invasion are the main difficulties when considering surgery of LG tumors. Because bone invasion occurs at an early phase in cancers of the region, surgery is supported by radiotherapy in most cases [3-8]. Tissue-sparing surgical techniques with low morbidity and reconstructive approaches followed by loco-regional conformal radiotherapy should be considered as an optimal therapeutic option. Some radiation oncologists recommend radiotherapy to all patients, including those who underwent complete resection. Others recommend radiotherapy in the presence of poor prognostic factors, including a T3 tumor, advanced stage, perineural invasion, basaloid subtype and a positive surgical margin. However, despite adjuvant radiotherapy, outcomes are still not promising [4, 7, 8].

Ongoing debate continues regarding tumor volumes and margins that can be treated by radiotherapy. In recent years, novel technological advances such as IMRT, IG-IMRT, neutron and proton therapies have reduced radiotherapy volumes and decreased radiation exposure to healthy tissue [9-12]. As Douglas et al. report, these sophisticated modalities are superior to conventional methods in treating LG tumors [6]. However, clinical experience is scarce in such modalities. Our patient underwent surgery 7 times, radiotherapy 3 times and systemic chemotherapy twice. Radiotherapy was given in case of a partial resection, recurrence and/or metastasis. This resulted in a complete response in dural and parenchymal metastases of brain, but only provided stable disease in bone metastasis. In addition the patient experienced an 8-month recurrence-free period after palliative radiotherapy.

Generally, chemotherapy is given to patients with recurrent or inoperable disease. Currently, chemotherapy is used as an adjuvant therapy to improve response and survival rates achieved by other therapeutic modalities. However, reports indicate that single- or multi-drug chemotherapy regimens are associated with low response rates and shorter remission periods [2, 9]. In our case, first systemic chemotherapy resulted instable disease. Despite shorter remission periods, it was thought that systemic chemotherapy was effective in disease control. However, disease progression was evident, as there was no response from the second chemotherapy treatment (paclitaxel).

In %80 of reported cases, recurrence surfaces within 5 years [4]. Factors influencing prognosis include age, gender, tumor localization, recurrence time, histological type, perineural and vascular invasion and positive surgical margin [1, 2, 5, 10]. In our case, disease progression persisted despite multi-modal therapy and the patient died 46 months after diagnosis.

Conclusion

Lacrimal gland ACC presents a therapeutic challenge despite its slow growth rate and lower likelihood of lymph-node metastasis. Postoperative radiotherapy with wide margins should be utilized—even after a complete resection—because of persistent recurrences, perineural invasion and hematogenous spread.

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