



# Metastatic Lacrimal Gland Adenoid Cystic Carcinoma to the Lung. Report of a Case with Multiple Recurrences and a Brief Review of the Literature

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## Abstract

Adenoid cystic carcinoma is a rare malignancy with historically high mortality and morbidity, although modern surgical techniques have led to improved outcome. Often disease course is complicated by persistent local, or distant recurrence, occurring up to 10-years following initial diagnosis. Here we describe a 63 year-old female who presented with a lacrimal gland mass, which proved to be adenoid cystic carcinoma. The mass was piecemeal resected and adjuvant radiation was administered. After multiple local recurrences and resections, lung metastasis was identified ten years following initial tumor diagnosis in the lacrimal gland.

Metastatic lacrimal adenoid cystic carcinoma is rare and there is no standard approach to management of metastases. Systemic therapy has had minimal benefit, however modern targeted therapies may provide additional options. There is evidence that patients who undergo metastasectomy can have improved survival. This case highlights the need for long-term follow up of patients with adenoid cystic carcinoma as well as the need for further evaluation for effective systemic therapy options.

**Keywords:** Adenoid cystic carcinoma; Lacrimal gland; Cancer survivorship; Molecular markers

## Abbreviations

ACC: Adenoid cystic carcinoma; MRI: Magnetic resonance imaging; CT: Computed tomography; EGFR: Epidermal growth factor receptor; HER-2: Human epidermal growth factor receptor 2; TTF1: Thyroid transcription factor; IHC: Immunohistochemistry; RT: Radiation therapy; OD: Oculus dextrus

## Introduction

Adenoid cystic carcinoma (ACC) is an uncommon malignancy first described in 1853 [1]. It most often arises in the minor salivary glands, and accounts for 10% of salivary gland tumors [2]. Rarely it can arise at other sites, with case reports describing primary sites in lung, breast, esophagus, and lacrimal gland [3,4]. Adenoid cystic tumor of the lacrimal gland is rare with an annual incidence of 1.3/1000000 and only half of these cases

are malignant. Of malignant lacrimal tumors, the majority are lymphomas, with 13.4% being ACC [5]. Historic data on this tumor showed a grim prognosis, with median survival ranging from 3-5 years, depending on tumor grade, and the primary treatment modality usually consisting of exenteration, which carries a high degree of morbidity [6]. Modern surgical techniques utilize a globe-sparing approach, which has led to improved quality of life [7]. Furthermore, utilization of adjuvant radiation therapy (RT) has been shown to have additional benefit at delaying local recurrence, providing survival benefit. Modern estimated disease-free survival is approximately 11 years. Despite these improvements, patients with ACC remain likely to have relapse both locally and distant [7,8].

In addition to local recurrence, ACC can metastasize, most commonly to the lung [9]. Unlike the management of the primary tumor and local recurrences, the management of metastatic disease is less clear [8]. Furthermore, there are no standardized guidelines for surveillance for metastatic disease. Historical data on patients with this cancer have shown the major causes of death are from cranial invasion or complications of metastases, most commonly from respiratory compromise due to pulmonary invasion [9]. Studies on various systemic therapies have not yet shown benefit and there is interest in targeted therapies, but evidence for these is limited at this time [10]. In this case report, we describe a patient with multiple local recurrences of lacrimal gland carcinoma who is later incidentally found to have pulmonary metastases displaying the nature of this malignancy as well as the current uncertainties with surveillance and metastatic management.

## Case Presentation

Patient is a 63 year old female who presented to clinic with complaints of right eyelid swelling. Patient began to have

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symptoms in her right eye 6 years prior. Her symptoms began with flashing lights, and shadows in right eye nasal quadrant. Two years later her right eyelid became sore to touch and pain progressed to include intermittent right sided headaches. On ophthalmologic exam, patient was found to have 5mm proptosis oculus dextrus (OD), along with inferior medial displacement of globe associated with limited abduction, and supraduction. Thyroid function tests were obtained, which were normal. Magnetic resonance imaging (MRI) was performed revealing a 2.4x2.0x2.3 cm extraconal mass in supratentorial right orbit. Computed tomography (CT) was performed two months later again demonstrating this mass and revealing remodeling and thinning of orbital roof and lateral wall of right orbit.

Patient was taken to OR for piecemeal resection, orbitectomy and reconstruction. A histopathological examination confirmed the diagnosis of adenoid cystic carcinoma with cribriform tubular growth patterns, and occasional solid sheets. The tumor cells were predominantly arranged in a cribriform growth pattern displaying several prominent pseudocysts surrounded by basaloid cells with hyperchromatic angulated nuclei (Figure 1A). Prominent perineural invasion was present (Figure 1B). Confirmatory immunohistochemistry (IHC) studies revealed that the tumor was p40 positive, CD 117 positive, S-100 positive (nuclear and cytoplasmic), GFAP negative, TTF1 negative, and HER2 negative, in support of the diagnosis of ACC. (Figure 1C). Staging CT at the time revealed scattered 5mm lung nodules in left upper and right middle lobes, which were deemed indeterminate, with recommendation for 3-6 month follow up, but no tissue examination was performed. Patient then received adjuvant proton beam radiation therapy (RT) (72 cGy in 36 fractions). CT of orbits performed 1 year later was negative for disease recurrence. Four years and then again seven years later, patient had local recurrence and had complete resection performed both times with safe surgical margins.

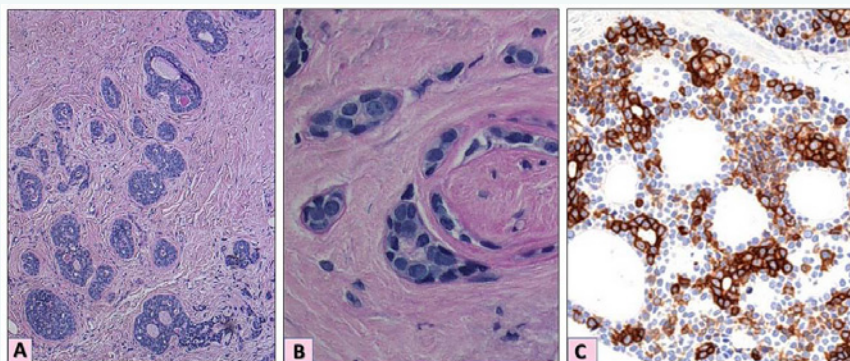
Ten years following initial diagnosis, patient had chest CT performed for symptoms of bronchitis, which was significant for three solid nodules in lung apices bilaterally, and right middle lobe largest measuring 1.6 cm. The largest mass was biopsied, and the histopathological examination confirmed the diagnosis of

metastatic adenoid cystic carcinoma with cribriform and tubular features. The histomorphology and immunohistochemistry profile was similar to the original primary carcinoma. After multidisciplinary discussion with tumor board, recommendation was to perform resection of metastases. The patient declined surgical intervention and has since been lost to follow up.

## Discussion

Due to its overall rarity, ACC of the lacrimal gland provides a challenge in regards to both diagnosis and management. Although salivary ACC is also an uncommon tumor, it occurs much more commonly than its lacrimal counterpart [11]. As the histomorphology of both tumors is similar, the backbone to diagnosis and treatment of lacrimal ACC utilizes the experiences and existing studies of salivary ACC [12]. Grading appears to be similar in all ACC with basaloid or solid histologic pattern conferring a poorer prognosis than criboform or tubular histology [13], the latter of which is described in this case. However, given its proximity to the eye, and propensity for peri-neural invasion at time of diagnosis, lacrimal ACC has its own unique complexities. Given the rarity of non-salivary ACC, randomized controlled trials are rare, and the current approach to management is based on retrospective review and extrapolation from salivary ACC management [8].

Early in the seventies, a small case series demonstrated that surgery with adjuvant RT was shown to have survival benefit and prolong time to recurrence [7]. In addition, advancements in surgical techniques have allowed for globe-sparing resection, but have not shown a difference in survival compared to exenteration. The combined effect of surgery and RT have led to more recent estimates of lacrimal ACC disease free survival to be 11 years [8]. These effects have not been able to prevent delayed relapse, as is exemplified in this case. Metastatic disease is now the primary cause of death, as systemic approaches with chemotherapy have not shown to provide significant sustained response and, in general, are not recommended<sup>10</sup>. Molecular studies have identified targets of treatment in the NOTCH1, NOTCH2, EGFR, erb2, HER2 pathways, among others however there is insufficient evidence to support utilization of targeted therapies at this time [10,15].



**Figure 1** Histopathology of initial lacrimal gland primary adenoid cystic carcinoma. A) The tumor shows predominately cribriform pattern with tubular and scattered solid areas (H&E stain X20). B) Prominent perineural invasion (H&E stain X60). C) Positive immuno staining with CD117.



Given the resistance of distant metastasis response to systemic therapies, and their negative effect on overall survival. Whether aggressive pulmonary metastasectomy (PM) improves survival is controversial, however, there is data to support survival benefit from resection of metastases, if their location is amenable, as in this case<sup>4</sup>. The definitive impact of complete lung metastasis resection on the course of the disease has yet to be fully determined following long series studies. The average survival after development of pulmonary metastases is 3-4 years. Hsueh-Ju Lu et al studied the most common head and neck carcinomas and the effectiveness of pulmonary metastasectomy. They used whole-exome sequencing for matched pulmonary metastatic samples. In their study, the genes where genetic variants have been identified, were sent for analysis by DAVID, IPA, and STRING. Forty-nine patients with primary head and neck malignancies were enrolled. Two-year post-metastasectomy survival rates of adenoid cystic carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma were 100%, 88.2%, 71.4%, and 59.2%, respectively [16].

This case provides a unique presentation of nodules present 10 years prior to resection and repeat imaging show a gradual progression. Although there was no initial pathologic examination of the earlier nodules, the clinical presentation of this case is highly compatible with progression of these nodules into larger nodules of metastatic adenoid cystic carcinoma. This is one acknowledged limitation of this case study. Other limitation is the possibility of a second primary adenoid cystic carcinoma arising from the lung, which cannot be completely ruled in, or ruled out. However, the presence of multiple nodules and progressive increase in size and behavior is in favor of metastatic carcinoma.

The rarity of lacrimal gland ACC and its aggressive nature presents a challenging diagnosis and management. Modern methods of treatment allow for preserved vision and extend survival, however advances are required to address metastatic disease and to determine appropriate screening for distant metastases. Cases like the one described above show the importance in continued surveillance for many years after the initial diagnosis as well as the current void in treatment options for systemic disease.

It is our hope that this report raises awareness of what remains an unmet need in optimal management and follow up of this type of uncommon metastatic carcinoma, and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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