Adenoid cystic carcinoma of the lacrimal gland is frequently characterized by *MYB* rearrangement

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Abstract

Purpose Adenoid cystic carcinoma (ACC) represents ~10–15% of salivary neoplasms and almost universally exhibits a lethal clinical course. ACC is also known to occur in the lacrimal gland. ACC is characterized by its heterogeneous morphology and may demonstrate tubular, cribriform, and/or solid architectural patterns. Unfortunately, these histopathological features are not specific to ACC and can be seen in other salivary gland-type neoplasms, introducing a diagnostic dilemma. The discovery of fusion transcripts has revolutionized the diagnosis, surveillance, and treatment of epithelial malignancies. In several anatomic subsites ACC is frequently characterized by a fusion transcript involving genes *MYB* and *NFIB*; more specifically, t(6;9)(q22-23;p23-24). This study explores the incidence of *MYB* rearrangement in cases of lacrimal gland ACC using fluorescent *in situ* hybridization.

Materials and methods Retrospective clinical and histopathological review of 12 cases of lacrimal gland ACC seen at Mayo Clinic over a 25-year period (1990–2015) was performed. Demographic and clinical data were obtained from medical records. Surgical pathology archival material including H&E slides and immunostains was re-examined. Formalin-fixed paraffin-embedded material was further evaluated using immunohistochemistry when appropriate. Fluorescent *in situ* hybridization (FISH) using a *MYB* break-apart probe was applied to all histologically confirmed cases of ACC and benign salivary gland parenchyma.

Results The median patient age was 53.6 years (range 12–64) and distributed equally by gender (six male and six female). Rearrangement of *MYB* was identified using

FISH in seven cases (58%). Twenty-five sections of benign salivary gland parenchyma showed no evidence of *MYB* rearrangement. Primary surgical resection was most common treatment, and 78% of the patient received adjuvant radiation therapy. Median overall survival (OS) was 11 years. Rearrangement of *MYB* did not affect OS.

Conclusions In summary, our results indicate that the *MYB* rearrangement defines a significant subset of lacrimal gland ACCs. Importantly, FISH for *MYB* rearrangement may be used as a diagnostic tool during pathological examination of lacrimal gland neoplasms. Our results showed no relationship between rearrangement status and clinical outcome. Lastly, the presence of t(6;9) in ACC may provide a platform for molecular-targeting strategies in the future. *Eye* (2017) 31, 720–725; doi:10.1038/eye.2016.307; published online 13 January 2017

Introduction

Primary lacrimal gland tumors are relatively rare—accounting for 5–25% of space-occupying orbital lesions.¹ Adenoid cystic carcinoma (ACC) has been reported to be the most common form of malignant epithelial lacrimal gland tumor, comprising approximately 66% of malignant lesions, and has been reported to have a 15-year survival rate of only 20%.^{2–4} In addition, ACCs of the lacrimal gland usually carry a poor prognosis due to osseous and/or perineural invasion.¹

Clinical features of lacrimal gland ACC include ocular pain in combination with globe dystopia, proptosis, and ‘S’ shaped ptosis. ACC is characterized by its heterogeneous histomorphology and may demonstrate tubular,

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cribriform, and/or solid architectural patterns.² Unfortunately, these histopathological features are not specific to ACC and can be observed in other salivary gland-type neoplasms, often posing a diagnostic dilemma for pathologists. Optimal patient management is controversial but includes globe-sparing surgery followed by external radiotherapy (RT), proton-beam therapy, intra-arterial chemotherapy, or radical orbital exenteration in select cases.^{5,6} The differential diagnosis for ACC includes benign and malignant entities such as pleomorphic adenoma, basal cell adenoma, basal cell adenocarcinoma, and polymorphous low-grade adenocarcinoma. Needless to say, accurate pathological classification is imperative for correct clinical management and prognostic implications.

The discovery of fusion transcripts has revolutionized the diagnosis, surveillance, and treatment of epithelial malignancies. In the context of salivary gland neoplasia, fusion transcripts are currently used to define and diagnose mucoepidermoid carcinoma, mammary analog secretory carcinoma of salivary glands, hyalinizing clear cell carcinoma, and ACC. Recently, ACC has been linked to a distinguishing cytogenetic abnormality, t(6;9) (q22-23; p23-24), resulting in a fusion between the gene encoding transcription factor *MYB* [v-myb myeloblastosis viral oncogene homolog (avian)] and *NFIB* (nuclear factor IB) transcription factor in 55–92% of cases from the salivary gland and breast.^{7–11} The suspected molecular result of this genetic alteration is activation of the *MYB* oncogene and associated target genes involved in cell growth, apoptosis, transcription, and cell cycle regulation.^{7,8} This genetic rearrangement carries potential utility for diagnostic, prognostic, and even therapeutic purposes as *MYB*-activated pathways are currently being explored.⁸

Currently, over 800 pediatric and adult cases of ACC of the lacrimal gland have been reported in literature. However, most of the articles only describe single cases or small case series due to the rarity of lacrimal gland ACC.^{3,4,12–14} In addition, the molecular pathogenesis of ACC in the lacrimal gland has yet to be widely reported. Recent literature has shown that the translocation between chromosomes 6 and 9 (q22-23; p23-24), is present in ACC of the breast and head and neck.⁷ However, little is known regarding *MYB-NFIB* genetic alterations in lacrimal gland ACC. Recent studies also suggest that *MYB* may be activated by other mechanisms other than gene fusion, thus further emphasizing the role of *MYB* in ACC of the lacrimal gland.^{7,8} We sought to identify the frequency of t(6;9)(q22-23;p23-24), involving *MYB* and *NFIB*, using fluorescent *in situ* hybridization (FISH) in cases of ACC specifically involving the lacrimal gland and to correlate the findings with clinical parameters and outcome.

Materials and methods

The study was approved by the Mayo Clinic Institutional Review Board. Cases of ACC between 1990 and 2015 were identified in the Mayo Clinic Anatomic Pathology database. Only cases of primary lacrimal gland ACC were included. Patients whose formalin-fixed paraffin-embedded tissue was not available for analysis were excluded from study.

Clinical data

Patients' medical records were reviewed and demographic and clinical data was abstracted including age at diagnosis, gender, primary tumor site, and treatment-related information (surgery, radiotherapy, and chemotherapy). To calculate survival end points, the date of diagnosis (biopsy or excision), date of recurrence (date of biopsy, or the date of imaging or clinic visit documenting relapse), and date of death or last follow-up were recorded.

Histopathology

Archival surgical pathology material was obtained for patients previously diagnosed with ACC of the lacrimal gland at Mayo Clinic Rochester between 1990 and 2015. Histopathologic analysis was performed by two surgical pathologists (MGK and JJG). Lacrimal gland ACC cases were classified according to the predominant architectural pattern (cribriform, solid, and tubular).

Cytogenetics

MYB rearrangement was analyzed with break-apart fluorescence *in situ* hybridization (FISH), as previously described by Roden *et al.*¹⁵ Human bacterial artificial chromosomes (BACs) flanking the *MYB* gene region were identified using the University of California Santa Cruz (UCSC) February 2009 Assembly hg19. The 5'*MYB* clones (CTD-2533B20, RP11-366H19 and RP11-63K22) were labeled by nick translation with Spectrum Orange dUTP (Abbott Molecular/Vysis Products, Abbott Park, IL, USA) and the 3'*MYB* clones (RP11-170P19, RP11-751F23 and RP11-259A7) were labeled with SpectrumGreen dUTP (Abbott Molecular/Vysis Products, Abbott Park, IL, USA). Labeled clones were then combined to create a dual-color fusion break-apart (BAP) probe set. The BAP probe set was applied to individual slides, hybridized, and washed according to the partially automated tissue (PAT) -reduced pepsin FISH protocol.

The slides were placed in a 90 °C oven for 15 min and then deparaffinized with xylene (two times, 15 min each)

at room temperature (RT), dehydrated in 100% ethanol for 5 min at RT, and placed in 10 mM Citric Acid (pH 6.0) and microwaved for 10 min. Following this, the slides were immersed in $2 \times$ standard saline citrate (SSC) for 5 min at 37°C followed by digestion in 0.2% pepsin working solution (1.2 grams pepsin/600 ml 0.9% NaCl pH 2.5) at 37°C for 12 min. Immediately after digestion, the slides were dehydrated using an ethanol series (70, 85, 100%) 2 min each at RT. Working solution of BAP MYB (Mayo Clinic Laboratory developed probe, Rochester, MN, USA) was made by mixing $1\mu\text{l}$ of concentrated 5' MYB probe and $1\mu\text{l}$ of concentrated 3' MYB probe with $8\mu\text{l}$ of LSI/WCP hybridization buffer (Abbott Laboratories, Abbott Park, IL, USA). The working solution was then applied to the target areas, cover slip added, co-denatured with a ThermoBrite (Abbott Park, IL, USA) at 83°C for 5 min, and hybridized overnight in a 37°C humidified oven.

Following hybridization, slides were soaked in RT $2 \times$ SSC/0.1% NP-40 to remove coverslips, placed in $2 \times$ SSC/0.1% NP-40 at 74°C for 2 min and then placed into RT $2 \times$ SSC/0.1% NP-40 for 2 min. The slides were stained with 4'-6-diamidino-2-phenylindole (DAPI) (Vector Laboratories, Burlingame, CA, USA) and coverslips were added again for microscopic review. Visualization of the FISH signals was accomplished by using fluorescence microscope and pictures were captured by using a FISH imaging system (CytoVision, Leica Biosystems, Buffalo Grove, IL, USA). Two experienced FISH technologists (DLK and SMK) independently scored 50 tumor nuclei for each case. A cutoff of $>5\%$ breaks was selected for a positive score.

Statistical analysis

Statistical analysis was performed using software JMP version 10.0 (SAS Institute, Cary, NC, USA). Survival statistics were calculated using the Kaplan–Meier method. In order to calculate OS, the date of diagnosis and date of death were used. If patient was alive or lost to follow-up then date of last follow-up was used for censoring.

Results

Histopathology

Median size of the tumor was 2.7 cm (1–6.5). In regards to the histological pattern of the 12 ACC cases, four were predominantly cribriform, three were predominantly solid, two were a mix of solid and cribriform, two were a mix of solid and tubular, and one was a mix of tubular and cribriform (Figure 1). Results are summarized in Table 1.

a

b

Figure 1 Histopathology of lacrimal gland adenoid cystic carcinoma. Case showing cribriform and tubular architectural patterns (a; H&E $\times 200$). Tumor is characterized by a dual population of myoepithelial and ductal cells (b; H&E, $\times 400$).

Cytogenetics

Rearrangement of MYB was identified using FISH in seven cases (58%; Figure 2). Rearrangement was noted in all architectural patterns (tubular, cribriform, and solid).

To confirm the specificity of MYB rearrangement for ACC, FISH was also performed on 25 sections of benign salivary gland parenchyma. No rearrangement of the MYB gene region was observed in these sections.

Clinical outcome

Out of the 12 cases of lacrimal gland ACC, six were female. The median age was 54.9 years (12–65) years. Ten (83%) patients had surgical resection of the tumor as primary treatment. One patient declined treatment and one patient had no follow-up after initial diagnostic biopsy. Out of the 10 surgical patients, three patients had tumors removed with negative margins (R0), six had

Table 1 Clinical, histologic, and cytogenetic features of lacrimal gland adenoid cystic carcinoma

Patient	Age at diagnosis/ gender	Architectural pattern	Local recurrence	Distant metastasis	MYB rearrangement	Follow-up time
1	65 M	Solid	Yes	No	Present	DOD
2	64 M	Solid/cribriform	Yes	Yes	Present	DOD
3	55 M	Solid/cribriform	No	No	Present	NED 40 months
4	41 F	Cribriform	No	No	Absent	DOD
5	13 M	Cribriform	No	No	Absent	Lost to follow-up after 54 months
6	55 F	Cribriform	Yes	No	Absent	AWD 137 months
7	61 F	Cribriform	No	No	Present	NED 10 months
8	53 F	Solid/tubular	No	No	Present	NED 11 months
9	23 F	Solid	Yes	Yes	Absent	AWD 39 months
10	22 M	Solid	No	No	Present	DOD
11	60 F	Solid/tubular	No	No	Absent	NED 11 months
12	56 M	Tubular/cribriform	No	No	Present	NED 11 months

Abbreviations: AWD, alive with disease; DOD, died of disease; NED, no evidence of death.

Figure 2 FISH of lacrimal gland adenoid cystic carcinoma. Case showing rearrangement of MYB (a). Case showing no rearrangement of MYB (b).

microscopic margins positive (R1) and one had gross residual disease at the completion of surgery (R2). Post operatively, seven (78%) patients received adjuvant radiation therapy, two patients did not, and one patient has no follow-up data after surgery. There were four locoregional recurrences and two patients developed distant disease after their surgical resection. Out of 12 patients, four have died of disease with median OS of 11 years for the whole cohort. Rearrangement of MYB did not affect OS.

Discussion

We identified MYB rearrangement in 58% of 12 cases of lacrimal gland ACC. Previous studies regarding lacrimal gland ACC are summarized in Table 2. Only one other study has shown a high frequency of MYB rearrangement in lacrimal gland ACC.³ von Holstein *et al*³ analyzed 14 patients with primary lacrimal gland ACC and 19 non-ACC lacrimal gland tumors using a dual-color break-apart FISH probe strategy. Their findings showed that seven out of 14 ACC cases showed MYB fusion, while all 19 non-ACC tumors displayed no fusion. Our results were similar to the findings by von Holstein *et al*,³ as well as to the findings by Brill *et al*,¹⁶ which identified a 44% frequency of MYB-NFIB fusion in ACC of multiple sites. The reason for variation in the frequency of detected MYB-NFIB fusion products is not entirely clear but likely multifactorial. Similar to von Holstein *et al*, our study used break-apart FISH probe strategy; Brill *et al* analyzed MYB-NFIB fusion products by RT-PCR. In addition, Brill *et al*¹⁶ found the fusion oncogene in 86% of ACC when using fresh frozen tissue in contrast to 44% when using FFPE tissue.

Table 2 Literature review of lacrimal gland ACC

Study (Year)	# of patients studied with ACC of lacrimal gland	Gender	Mean age at diagnosis, years (range)	# of patients alive without disease after treatment	Median follow-up, years (range)	Mean survival time
Font <i>et al</i> ¹²	13	9M, 4F	44 (14–80)	2	8.5 Years (1–16 years)	4.5 Years from time of initial surgery
Perez <i>et al</i> ¹⁴	12	6M, 6F	40.4 (19–52)	4	N/A	77.8 Months from time of completion of treatment
Esmaeli <i>et al</i> ⁴	20	6M, 14F	39.5 (10–68)	6	34 Months (6–264 months)	18 Months from time of completion of treatment
Williams <i>et al</i> ¹³	18	8M, 10F	43 (9–69)	10	26.5 Months (6–102 months)	N/A
von Holstein <i>et al</i> ³	14	7M, 7F	43 (23–67)	5	7 Years (1–27 years)	Median tumor-specific survival was 8.6 years

MYB rearrangement is considered highly specific for ACC and therefore helpful in the distinction of lacrimal gland ACC from other salivary gland carcinomas. This distinction is important as differences in prognosis and treatment are dramatic. Lacrimal gland ACC cases are reported to have a 15-year survival of 20%.^{2–4,17} A study by Font *et al* (1998) showed that all 12 out of the lacrimal ACC cases had local recurrences ~3.5 years after surgical treatment.¹²

In support of the high specificity of t(6;9) for ACC, Mitani *et al* studied 34 non-ACCs of the salivary gland including myoepithelial carcinomas, acinic cell carcinomas, mucoepidermoid carcinomas and salivary duct carcinomas, polymorphous low-grade adenocarcinomas, and epithelial-myoepithelial carcinomas. In this study, none of these tumors harbored the t(6;9).⁸ West *et al* also evaluated a wide variety of non-ACC salivary gland tumors that included myoepithelioma, epithelial-myoepithelial carcinoma, pleomorphic adenoma/cellular pleomorphic adenoma/carcinoma ex pleomorphic adenoma, oncocytic hyperplasia/oncocytoma/oncocytic carcinoma, basal cell adenoma/adenocarcinoma, salivary duct carcinoma, and adenosquamous carcinoma as well as tumors similar to those studied by Mitani *et al*.⁹ Each of these tumors was negative for *MYB* rearrangement or fusion as well. Of note, only a single case of a polymorphous low-grade adenocarcinoma has been reported to harbor the t(6;9).¹⁸ We sought to confirm the specificity of *MYB* rearrangement for ACC in the lacrimal gland and to confirm its utility in the distinction from potential morphological mimickers in the lacrimal gland.

To test the specificity of t(6;9) for ACC, we also evaluated 25 cases with benign salivary gland parenchyma. We did not identify *MYB* rearrangement in any of these cases, providing additional evidence for the specificity of this genetic signature and its clinical utility in making the diagnosis of lacrimal gland ACC. However, although highly specific for ACC, the lack of this finding does not exclude a diagnosis of lacrimal gland ACC,

given that *MYB* rearrangement is only present in a subset of these tumors.

The association of *MYB-NFIB* fusion with clinical features and prognosis of ACC, if any, is not entirely clear. Our results did not show any association between the presence of *MYB* rearrangement in lacrimal gland ACC and OS. Although our study sample size is relatively low in comparison with studies of other primary lacrimal gland carcinomas, it is quite large for lacrimal gland ACC given its overall rarity. These cases were collected over a 25-year period at a large institution. Therefore, a multicenter study is likely required to study an even larger population of ACC of the lacrimal gland to conduct reliable multivariable analysis.

The classic t(6;9) translocation may not only serve diagnostic purposes, but may potentially be of therapeutic value given its relatively high prevalence in lacrimal gland ACC. Although targeting *MYB*'s transcriptional function itself is challenging, targeting molecules that are affected downstream of t(6;9) appears more promising. Studies by Moskaluk *et al*¹⁹ showed that low-passage primary ACC xenografts express spontaneously activated FGFR-1 receptors. This growth factor has been found to be upregulated in ACC cells with *MYB* overexpression and therefore is a candidate downstream effector of this oncoprotein.^{7,20} In fact, clinical trials targeting FGF or FGFR in ACC are currently underway.²¹ Other potentially targetable downstream effectors of *MYB* include cell proliferation proteins (MYC, CD53, FGF2, VEGFA, KIT), cell cycle proteins (CCNB1, CDC2, MAD1L1), apoptosis-related markers (AP15, BCL2, BIRC3, HSPA8, SET) and cellular adhesion molecules (CD34), some of which are already targeted in clinical trials.^{21,22}

In conclusion, FISH for *MYB* rearrangement may be used as a diagnostic tool during the pathological examination of lacrimal gland neoplasms. However, a negative result does not rule out the possibility of lacrimal gland ACC. *MYB* rearrangement does not appear to be associated with prognosis of lacrimal gland ACC.

However, multicenter studies might be helpful to confirm that finding in a larger patient population for robust statistical analysis. Lastly, the presence of t(6;9) in ACC may provide a platform for molecular-targeting strategies in the future.

Summary

What was known before

- In several anatomic subsites, adenoid cystic carcinoma (ACC) is frequently characterized by a fusion transcript, t(6;9)(q22-23;p23-24). The incidence of MYB rearrangement in cases of lacrimal gland ACC is unknown.

What this study adds

- Fluorescent *in situ* hybridization for MYB rearrangement may be used as a diagnostic tool during pathological examination of lacrimal gland neoplasms to confirm the diagnosis of adenoid cystic carcinoma (ACC). The presence of MYB rearrangement in lacrimal gland ACC may provide a platform for molecular-targeting strategies in the future.

Conflict of interest

The authors declare no conflict of interest.

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