STRN-ALK Fusion in Advanced Salivary Gland Carcinoma With Response to Anaplastic Lymphoma Kinase Inhibition: Case Report and Literature Review

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ABSTRACT

Salivary gland carcinomas are a heterogeneous group of rare tumors. There is no established standard of care therapy for metastatic disease. We describe the case of a patient with metastatic salivary gland adenocarcinoma harboring *STRN-ALK* translocation, with tumor response and clinical benefit from anaplastic lymphoma kinase (*ALK*) inhibition. Our patient experienced clinical benefit from first and second generation *ALK* inhibition in a chemotherapy refractory tumor. Tumor mutation profiling can identify mutations that may render tumors sensitive to targeted therapy with tyrosine kinase inhibitors.

INTRODUCTION

Salivary gland carcinomas are heterogeneous tumors that affect less than 2500 adults in United States annually.[1] While the era of precision oncology has transformed the treatment paradigms for solid tumors like non-small cell lung cancer (NSCLC) and melanoma, the development of biomarker-driven therapy for advanced salivary gland tumors remains challenging due to rarity of the disease and limited actionable targets.[2,3] Treatment of metastatic disease is still mostly based on chemotherapy, despite the low response rates. Recent availability of targeted therapies, such as *NTRK* inhibitors, has been a welcome addition to treatment options, but they represent less than 5% patients with salivary gland adenocarcinomas, not otherwise specified (NOS).[4] We present a challenging case of aggressive salivary gland adenocarcinoma with dramatic, clinically meaningful response to *ALK* inhibition.

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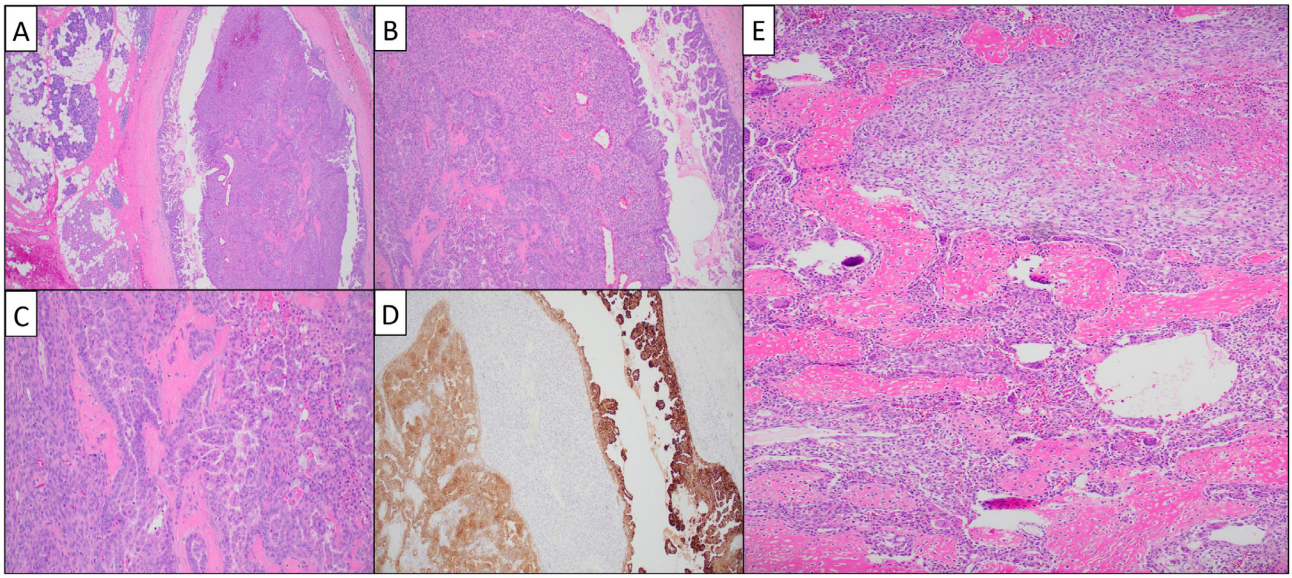
CASE PRESENTATION

A 50-year-old White male was diagnosed initially with AJCC (American Joint Committee on Cancer) 7th edition stage IVA (pT1pN2bcM0) adenocarcinoma NOS of the right parotid gland, for which he underwent right parotidectomy and right neck dissection. Pathology review showed a 1.5 cm unifocal adenocarcinoma with papillary and micropapillary architecture and focal spindle features (Figure 1). Sixteen of the 64 lymph nodes examined were positive, with largest nodal diameter of 3.5 cm with extracapsular extension. Other notable features included presence of perineural invasion and lymphovascular invasion (LVI). Immunohistochemical (IHC) stains showed tumor expression of pankeratin, mammaglobin, and S100 with focal p16 immunoreativity. Fluorescence in situ hybridization (FISH) showed intact *ETV6*, *RET*, and *MAML2* genes. He received adjuvant chemoradiotherapy (66Gy in 33 fractions together with weekly carboplatin and paclitaxel) and subsequently pursued close surveillance with clinical examination every 3 months and scans every 6 months.

Three years after his initial surgery, the patient developed right cervical and axillary nodal recurrence, for which he underwent right radical and central neck dissection and right axillary dissection. Pathology showed metastatic adenocarcinoma, morphologically similar to the prior parotid tumor. Similarly, LVI and extracapsular extension were identified again. Additional workup showed no immunoreactivity for the androgen receptor by IHC, an intact *NTRK1* gene by FISH, and no amplification of HER2 by chromogenic in situ hybridization. PD-L1 IHC was negative. He received additional hyperfractionated radiotherapy regimen (45Gy in 30 fractions) to the right neck and axilla.

Seven months later, the patient again presented with new

Figure 1. Microscopic Images



A) Low-power hematoxylin and eosin (H and E) image demonstrating the tumor interface to the background parotid parenchyma; B) Medium-power H and E image highlighting the epithelioid component and adjacent spindle cell component of the tumor; prominent papillary architecture is accentuated at the periphery of the tumor; C) High-power H and E image showing tumor cells with abundant eosinophilic cytoplasm and occasional mucinous differentiation; D) Mixed cytokeratin immunohistochemical stain is diffusely and strongly expressed in the epithelial component and is absent in the sarcomatoid component; E) H and E section of the recurrent tumor demonstrates sheets of epithelioid to spindled tumor cells. Islands of malignant osteoid admixed with osteoclast-like giant cells are prominent. Necrosis and lymphovascular space invasion are frequent. An epithelial component is notably absent in the recurrent tumor.

right cervical adenopathy, right lower neck subcutaneous mass, and left supraclavicular adenopathy. Fine needle aspiration cytology from the left supraclavicular lymph node showed metastatic adenocarcinoma, consistent with his prior parotid tumor. Computed tomography of the lung showed up to 0.2 cm bilateral lung micronodules that were indeterminate but new compared to his scans 7 months prior. Due to lack of clinical trial availability, his tumor was sent for FoundationOne testing. This revealed a microsatellite stable tumor and the presence of a *STRN* (NM_003162)-*ALK* (NM_004304) fusion (S2; A20). He was started on crizotinib therapy and tolerated it with minimal side effects, most notably mild nausea and diarrhea. His follow-up scans 2 months after crizotinib initiation showed interval tumor response (Figure 2).

Subsequent 2-month follow-up scans showed interval progression in the right neck mass, despite continuation of crizotinib. A core needle biopsy of the right neck lesion showed metastatic carcinoma. He underwent wide excision of the right neck mass and right neck dissection. Pathology review of the surgical excision specimen showed sarcomatoid carcinoma, with osteosarcomatous differentiation characterized by islands of malignant osteoid admixed with multinucleated osteoclast-like giant cells in a background of high-grade epithelioid to spindled cells (Figure 1E). The tumor sample was again sent for FoundationOne testing and showed a *STRN* (NM_003162)-*ALK* (NM_004304) fusion (S2; A20) but no additional mutations. He started cytotoxic chemotherapy with cyclophosphamide, Adriamycin, and cisplatin and experienced marked progression following cycle 2 (Figure 3A1 and A2). He was subsequently started on alectinib and experienced marked improvement in his disease burden (Figure 3B and 3C). Clinically, he noted significant improvement in his pain, bleeding, and tenderness of skin/subcutaneous nodules and improved energy. He also was able to stop his opioid pain medications, which enabled him to continue his employment. He remained in remission for 12 months, after which he had rapid disease progression and subsequently elected to pursue hospice care.

DISCUSSION

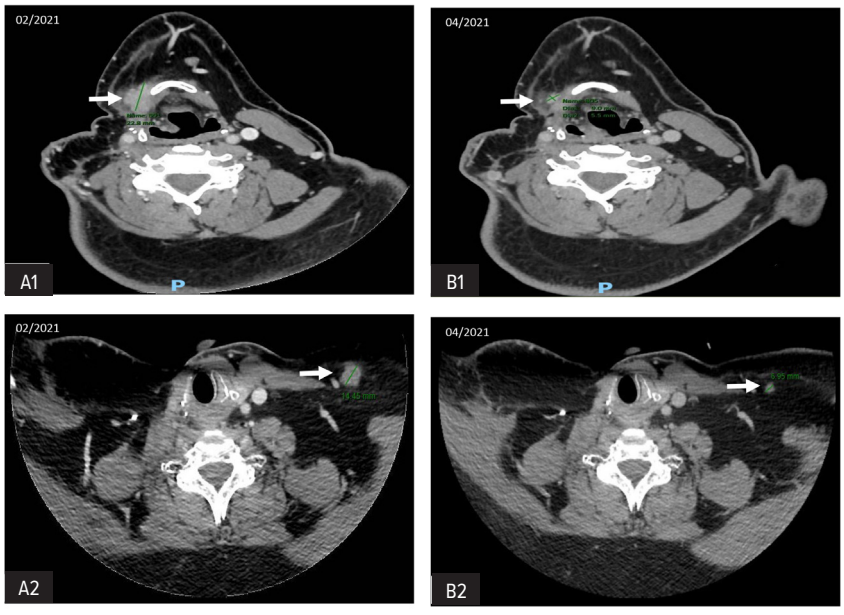
Chromosomal rearrangements in *ALK* are well-described targets for specific tyrosine kinase inhibitors (TKI) in lung cancer. *ALK* encodes a receptor tyrosine kinase whose activation induces downstream pathways associated with cell proliferation, cell survival, and angiogenesis. Oncogenic *ALK* fusions involve an N-terminal partner gene that promotes activation of *ALK* domain by dimerization.[5] More than 90 fusion partners for ALK have been identified in NSCLC.[6] The striatin (*STRN*) gene is an uncommon fusion partner of *ALK* rarely reported in solid tumors.[7,8] STRN is located on the short arm of chromosome 2—the same location as the more common fusion partner echinoderm microtubule-associated protein-like 4 gene (*EML4*). The *STRN-ALK* fusion involves chromosomal translocation of exons 1 to 3 of *STRN* to exons 20 to 29 of fusion partner ALK

within the short arm of chromosome 2.[1] *STRN-ALK* fusion has been associated with an aggressive tumor behavior in solid tumors.[8] Only 9 cases of ALK –fusion-positive salivary gland carcinomas have been reported previously (Table).[5-9] To our knowledge, this is the first reported case of *STRN-ALK* fusion in metastatic salivary gland cancer with response to *ALK* inhibition therapy.

Although genetic alterations are frequent in advanced salivary gland carcinomas, *ALK* rearrangements are rare.[9-13] Salivary gland carcinoma with *STRN-ALK* alteration has been described to have a cribriform histology and mucinous differentiation.[7] Our patient harbored a parotid gland tumor with unique morphologic features, including prominent papillary and micropapillary architecture with oncocytic and focal mucinous differentiation.

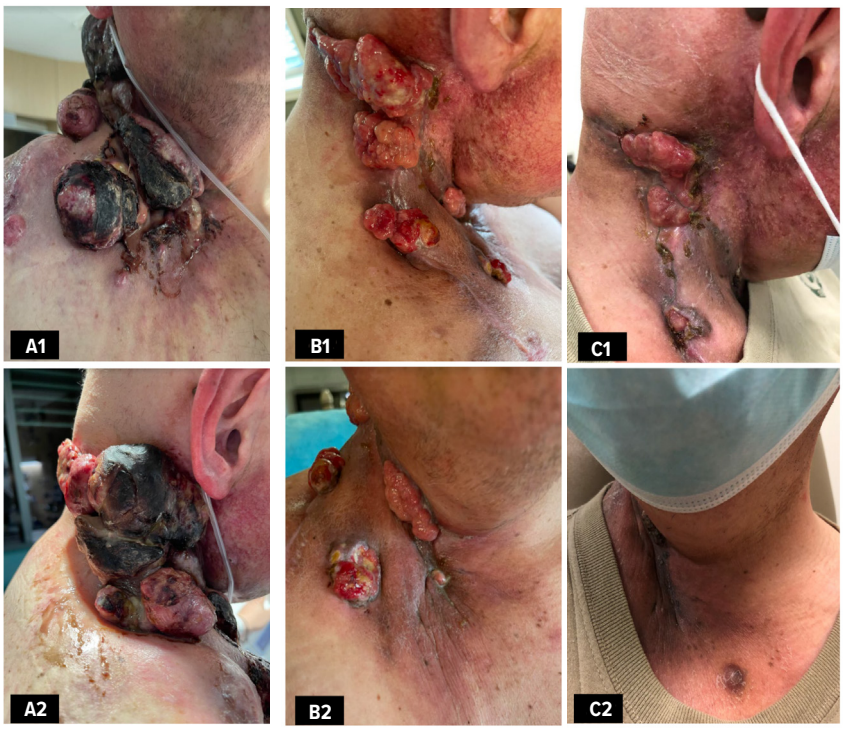
ALK fusions are effective therapeutic targets in lung cancer. Whether they represent a therapeutic target in salivary gland carcinomas has not been well established. Multiple *ALK* fusion types respond variably to *ALK*-TKIs. Crizotinib is a potent ATP-competitive inhibitor of the *ALK* and *MET* kinases and is approved by the US Food and Drug Administration (FDA) as therapy for *ALK-EML4* fusion NSCLC. It shows a therapeutic response in approximately 57% of patients with *ALK* rearrangement positive NSCLC.[14] Rare case reports in NSCLC patients also have shown sensitivity of this fusion peptide to crizotinib.[15] Both a clinical response[16] and lack of a response have been described with alectinib in *STRN-ALK* fusion-positive non-small cell lung cancer.[17] Our patient experienced a measurable, albeit short-lived, response with crizotinib and subsequently attained marked decline in clinical tumor burden with alectinib.

Figure 2. Computed Tomography Soft Tissue Neck With Contrast Images



A1 and A2: Prior to crizotinib initiation; B1 and 1B2: 2 months after crizotinib initiation.

Figure 3. Clinical Images



A1 and A2: Prior to alectinib initiation; B1 and B2: 2 weeks after alectinib initiation; C1 and C2: 4 weeks after alectinib initiation.

The standard of care management of metastatic salivary gland tumors is not well established. Chemotherapy has been utilized in patients with symptomatic or progressive disease affecting quality of life performance status with a goal to achieve cytoreduction. But whether chemotherapy alters the natural history of most salivary gland cancers subtypes remains unclear as trials employing chemotherapy have not shown improvement in overall survival. More recently,

Table. *ALK* Fusion-Positive Salivary Gland Carcinoma Cases Described in Literature

Case	Age/Sex	Subsite	*ALK* Fusion Partner	Salivary Gland Carcinoma Subtype	Treatment	Clinical Course
1[7]	NA	Parotid	*EML4-ALK*	Salivary ductal carcinoma de novo	NA	NA
2[7]	NA	Parotid	*HNRNPH3-ALK*	Salivary ductal carcinoma de novo	NA	NA
3[8]	82/M	Parotid	*CTNNA1-ALK*	Secretory carcinoma of salivary gland dissection	Surgical resection and selective neck	Indolent
4[9]	84/F	Intra-parotid lymph node	*STRN-ALK*	Salivary intra-ductal carcinoma	Surgical resection	Indolent
5[5]	73/F	Minor salivary gland of lip	*MYO18A-ALK*	Salivary intraductal carcinoma/low grade cribriform cystadenocarcinoma	Surgical resection`	Indolent
6[6]	67/M	Parotid	*STRN-ALK*	Salivary ductal carcinoma	Surgical resection, then palliative therapy following recurrence	NA
7[6]	79/M	Parotid	*EML4-ALK*	Salivary ductal carcinoma	Surgical resection	NA
8[6]	72/M	Parotid	*EML4-ALK*	Salivary ductal carcinoma	Surgical resection, then palliative chemotherapy	NA
9[6]	69/F	Parotid	*EML4-ALK*	Intercalated-type intraductal carcinoma	NA	NA
10[a]	46/M	Parotid	*STRN-ALK*	Adenocarcinoma NOS	Surgical resection, chemo-radiotherapy, Crizotinib, Alectinib	Aggressive

Abbreviations: NA, not available; NOS, not otherwise specified
[a]Index case described in this report.

RET fusion TKI and NTRK fusion TKI larotrectinib have received site agnostic FDA approvals.

In the absence of a standard of care therapy for metastatic salivary gland cancer without *NTRK* or *RET* fusion mutations, we obtained FoundationOne medicine genetic analysis for our patient and identified a rare *STRN-ALK* fusion in his tumor. Since the tumor sent for analysis was a surgical specimen from his initial surgery, this rare fusion was likely an early event in tumorigenesis. Given his noticeable clinical and radiographic response, *STRN-ALK* fusion in this patients' tumor was likely the oncogenic driver as well. There were other important considerations for our patient before crizotinib could be initiated. Due to QTc prolongation and CYP3A inhibition with critozinib, his antidepressant was switched from escitalopram to paroxetine, and statin therapy had to be switched from simvastatin to rosuvastatin. He tolerated both of these medication changes well. Thus, clinicians should keep these important drug interactions in mind while using critozinib. The patient's subsequent clinical benefit to second like *ALK* inhibition with alectinib also demonstrates the utility of considering additional *ALK* inhibition following progression on first generation *ALK* inhibitors, such as crizotinib. Our patient experienced prolonged response to alectinib; thus, considering second generation *ALK* inhibitors in the front line may be a reasonable approach.

CONCLUSIONS

Tumor mutation profiling can yield potentially targetable mutations and should be considered in rare tumors with limited standard of care options. This is particularly important given the expanding repertoire of targeted therapeutic agents.

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