Diagnostic challenges and successful organ-preserving therapy in a case of secretory carcinoma of minor salivary glands

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Funding information
postdoc.mobility fellowship of the Swiss National Science Foundation, Grant/Award Number: P400PM_183852

Abstract

Background: Secretory carcinoma is a more recently described subtype of salivary gland carcinoma that may pose diagnostic challenges and frequently harbors NTRK fusions that may successfully be targeted by TRK inhibitors in advanced disease.

Case: We present the case of a female patient with secretory carcinoma arising in the base of tongue with persistent disease after debulking surgery and definitive chemoradiation. As an alternative to salvage surgery, which would have resulted in significant impairment of swallowing and speech function, a targeted therapy with the TRK-inhibitor larotrectinib against an identified ETV6-NTRK3 fusion product was initiated. Larotrectinib treatment has been well tolerated, resulted in durable complete response and the patient maintains good swallowing and speech function.

Conclusion: The presented case underscores the importance of the accurate diagnosis of secretory carcinoma. It further highlights the impact of molecular testing as targeted therapies may play an important role in the management of advanced salivary gland cancers.

KEYWORDS
head and neck cancer, larotrectinib, minor salivary glands, NTRK fusion, secretory carcinoma

1 | INTRODUCTION

Secretory carcinomas (SC) of the salivary gland were classified over a decade ago, initially thought to be a more aggressive subtype of acinic cell carcinoma that bore some homology to secretory carcinomas of the breast. Initially classified as mammary analogue secretory carcinomas (MASC),1 the term was revised in the most recent edition of the WHO classification of Head and Neck Tumors (2017).2 In addition, the initial characteristic t(12;15) (p13;q25) translocation resulting in the ETV6-NTRK3 fusion transcript has been noted in these tumors, and more recently, occurring with some regularity associated with RET fusions.3,4 This tumor typically occurs in the major salivary glands; however, SC can also occur in atypical locations arising in minor salivary glands.5,6 The histopathologic diagnosis of SC may be
challenging, although it is more commonly recognized since its classification. Initially identified as an aggressive subset of acinic cell carcinomas, it is now recognized to be a more indolent tumor, but with a spectrum of clinical behavior. Although most SC may develop over years, cases with an aggressive disease course, including lymph node metastases along with local recurrence or even distant metastases with lethal outcomes have been reported.\(^1,7\) The rare occurrence of high-grade transformation in SC of major and minor salivary glands is often associated with an unfavorable prognosis.\(^8\)

Curative treatment strategies for SC of the salivary glands are identical to those of other salivary gland tumors concentrating on complete surgical resection. Dependent upon tumor stage and specific pathological features such as grade, perineural- and lymphovascular invasion and margin status, additional therapeutic modalities are considered, including adjuvant radiotherapy or chemoradiation. In the case of local recurrence or persistent disease of previously irradiated tumors, surgery, reirradiation or chemoradiation are the therapies of choice.\(^9\) Based on the frequency of fusion kinases associated with these tumors, nearly all, they are ideal candidates for targeted therapy,\(^1,3,4,7\) especially in the setting of advanced, recurrent or palliative disease. With the dominant ETV6-NTRK3 fusion, this tumor entity appears as an ideal candidate for inhibitors targeting tropomyosin receptor kinase (TRK) proteins, like the small-molecules larotrectinib or entrectinib. Indeed, larotrectinib and entrectinib therapy both induced rapid and durable relevant clinical activity in NTRK fusion-positive solid tumors including cases of salivary SC with locally advanced or metastatic disease.\(^10\)–\(^12\)

In this case report, we discuss the challenges of the proper diagnosis of SC, and the use of larotrectinib in a potentially salvageable recurrent tumor that would otherwise have exceptionally debilitating outcomes if surgically resected.

## CASE PRESENTATION

A 56-year-old White female was referred to her local otolaryngologist for further evaluation of a chronic sore throat lasting several months that failed conservative management. The otherwise healthy woman reported a personal history of 10 pack years of cigarette smoking until about 35 years prior and continued moderate alcohol intake (3–4 drinks per week). Laryngoscopy showed a mass likely originating from the base of tongue (BOT) that was biopsied and determined to be malignant. Histopathologic work up including immunohistochemical analysis revealing diffuse positivity for cytokeratin 7, weak, non-specific staining for GATA3 and mammaglobin, S-100, keratin 5/6 (Figures 2E–D). Immunohistochemistry revealed diffusely positive staining for GATA3, mammaglobin, S-100, keratin 5/6 (Figures 2E–H), and keratin 7. Tumor cells were negative for p40, ERG, desmin and smooth muscle actin. The case was diagnosed as a high-grade secretory carcinoma with molecular testing requested. This subsequently showed a confirmatory ETV6-NTRK3 fusion transcript involving ETV6 exon 5 and NTRK3 exon 15. Potential treatment options were discussed with the patient, including the standard treatment involving salvage surgery. Given that salvage surgery would be quite morbid including laryngectomy and glossotomy with for the patient significant functional impact, alternative therapy with an TRK-inhibitor was discussed as a potential function-preserving treatment strategy. The patient proceeded with the small molecule TRK-inhibitor larotrectinib. Larotrectinib was initiated and was administered at a dose of 100 mg BID. Although an initial radiographic assessment following 1.5 months on larotrectinib therapy showed no significant decline in tumor burden, following 4.5 months of treatment, a complete
Clinical response was seen by CT scan. In addition, larotrectinib was very well tolerated by the patient with no adverse serological features. The patient’s speech was well-maintained with no difficulty swallowing. At the time of this report, the patient has been on continuous Larotrectinib for 13 months, currently with a maintained complete response (Figure 1B). She continues on this therapy with regular clinical and radiographic follow up visits until the potential occurrence of evasive resistance.

**Figure 1** Treatment with larotrectinib resulted in complete resolution of the persistent secretory carcinoma of the left BOT (A, arrow) as illustrated with representative T1 TSE MRI images (3 mm slices) before initiation of larotrectinib therapy (A) and in the most recent imaging study after 11 months on therapy (B).

**Figure 2** Hematoxylin and Eosin stains of the patient’s initial biopsy of the primary tumor (A and B; 200X magnification), the persistent lesion of the BOT 6 months later (C; 400X) and of a second biopsy of the same persistent tumor taken in the midline vallecula region an additional 3 weeks later (D; 400X). Panel (A) shows focal papillary architecture with fibrovascular cores often associated with secretory carcinomas and tumor cells contain enlarged, hyperchromatic nuclei. The three sequential biopsies shown in panels (A–D) are consistent with morphologic features of secretory carcinoma: sheet-like morphology with foci of cytoplasmic clearing and pink (eosinophilic) cytoplasm with variably dense nuclei showing conspicuous nucleoli. Immunohistochemistry of the midline vallecular biopsy of the persistent tumor shows positive nuclear staining in tumor cells for GATA 3 (E, 400X), and cytoplasmic staining for mammaglobin (F, 400X) and S100 (G, 400X). Panel H shows intact surface epithelial staining (left) for squamous/myoepithelial marker keratin 5/6 with the tumor (right) showing multifocal positivity (200X). The immunohistochemical findings support a diagnosis of high-grade secretory carcinoma (with supporting molecular features of an ETV6-NTRK3 fusion gene).

**3** | DISCUSSION

As in the presented case, misclassification of salivary gland tumors is not uncommon, especially with small biopsies or when tumors present in atypical sites. Most commonly, SC have been traditionally associated with acinic cell carcinoma (AcCC), as they have some overlapping morphological and architectural features, including a microcystic growth pattern, solid sheets of cells and micropapillae.
but less so as pathologists become more familiar with its diagnosis. In contrast to most AcICC, typically diffusely positive for DOG1 (discovered on GIST-1) by immunohistochemistry, SC are typically diffusely positive for S-100, mammaglobin, and GATA3 and negative for DOG1. In addition, the detection of a fusion kinase, ETV6-NTRK3 in most SC of salivary glands and ETV6-RET in a significant subset, confirms the diagnosis. This characteristic chromosomal translocation can be detected by reverse transcription-polymerase chain reaction (RT-PCR), targeted fusion transcript detection by next generation sequencing or fluorescence in situ hybridization (FISH). In routine clinical settings without the option for molecular evaluation, diagnosis will need to focus on strict morphological criteria including a limited immunohistochemical panel if possible. Use of a pan-TRK antibody for immunohistochemistry can provide some aid in the differential diagnosis of SC versus AcICC, but the antibody, although specific, is not particularly sensitive, and given additional fusion partners, an initial screen would benefit more from DOG1/S100 in the differential, raising follow up testing once a diagnosis of SC is suspected, especially in any case of advanced disease or when the patient is a poor surgical candidate for other reasons. And, as described, although the ETV6-NTRK3 fusion represents the most common genomic aberration in SC of salivary glands, there are oncogenic rearrangements of ETV6 with fusion partners other than NTRK3, such as MAML3 or RET, and cases without ETV6 fusions have been described.

Whereas in the curative stage, surgery with appropriate adjuvant treatment represents the best treatment modality, in the case of unresectable or metastatic disease, targeted therapy with TRK-inhibitors represents a highly active therapeutic opportunity. In a pooled analysis of unresectable or metastatic disease, targeted therapy with TRK-inhibitors was associated with a complete response, respectively, upon larotrectinib treatment at a dose of 100 mg BID as administered in the presented case. In patients that responded to the treatment, the median duration of response was 35.2 months. As the development of resistance to TRK-inhibitors is likely, a continuous clinical and radiographic follow up is important. Both, on- and off-target resistance mechanisms to TRK inhibitors in solid TRK-fusion positive tumors have been reported. On-target mutations affect the TRK-kinase domain and thus restrict drug binding, and can potentially be circumvented by second-generation TRK inhibitors such as LOXO-195 that is currently evaluated in a clinical trial including NTRK fusion positive solid tumors with intrinsic or evasive resistance to a prior TRK inhibitor (NCT03215511). In contrast, off-target mutations typically cause resistance to second-generation TRK inhibitors and can occur during treatment with first- and second-generation TRK inhibitors. Different off-target genomic alterations that cause activation of the mitogen-activated protein kinase (MAPK) pathway or MET amplification have been reported. Thus, in the presented case, in the event of evasive resistance, a biopsy of the emerging lesion will be critical to determine the molecular mechanism of resistance. Based upon updated genetic alteration data, a follow up treatment strategy will be employed, including further targeted therapies or salvage surgery.

The era of targeted therapies in oncology opens avenues for creative treatment approaches in selected clinical situations. In the presented case, salvage surgery as the standard treatment option of this persistent SC of minor salivary glands would have been technically feasible, yet likely led to significant impairment of the patient’s quality of life. As the response rate of TRK-inhibitors in TRK-fusion positive solid tumors is substantially high, a treatment attempt to either downstage the tumor in the case of a partial response to facilitate surgery, or, as in the presented case, due to the complete response that will significantly delay repeat surgery until the likely recurrence of evasive resistance is quite appealing, and as shown in this case, quite successful.

**ACKNOWLEDGMENT**

R.B. was funded by a postdoc. mobility fellowship of the Swiss National Science Foundation (SNSF; P400PM_183852).

**CONFLICT OF INTEREST**

M.J.P. has served as a consultant for Aileron Therapeutics, AstraZeneca, Cygnal Therapeutics, Elstar Therapeutics, ImmuneOncia, KSQ Therapeutics, Merck, Siamb Therapeutics, Third Rock Ventures. The wife of R.B. is an employee and stockholder of CSL Behring. These commercial relationships are unrelated to the current study.

**AUTHOR CONTRIBUTIONS**

Conceptualization; data curation; investigation; project administration; resources; visualization; writing-original draft; writing-review & editing, R.B.; Data curation; resources; writing-review & editing, D.D.; Supervision; visualization; writing-review & editing, M.P.; Conceptualization; data curation; resources; supervision; visualization; writing-review & editing, P.S.; Conceptualization; data curation; project administration; resources; supervision; visualization; writing-original draft; writing-review & editing, J.C.P.

**ETHICS STATEMENT**

Written informed consent was obtained from the patient. The institutional approval was waived by the Institutional Review Board for this single patient case report.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**REFERENCES**

1. Skalova A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol*. 2010;34:599-608.
2. El-Naggar AK, JKC C, Grandis JR, Takata T, Sloat PJ. WHO Classification of Head and Neck Tumours. Lyon, France: International Agency for Research on Cancer; 2017.
3. Petersson F, Michal M, Ptáková N, Skalova A, Michal M. Salivary gland mucinous adenocarcinoma with minor (mammary analogue) secretory and low-grade in situ carcinoma components sharing the same ETV6-RET translocation and with no other molecular genetic aberrations detected on NGS analysis. Appl Immunohistochem Mol Morphol. 2020;28:e53.

4. Skalová A, Banečková M, Thompson LDR, et al. Expanding the molecular spectrum of secretory carcinoma of salivary glands with a novel VIM-RET fusion. Am J Surg Pathol. 2020;44:1295-1307.

5. Paudel D, Nishimura M, Adhikari BR, et al. Secretory carcinoma of minor salivary gland in buccal mucosa: a case report and review of the literature. Case Rep Pathol. 2019;2019:2074504.

6. Alves LDB, de Melo AC, Farinha TA, et al. A systematic review of secretory carcinoma of the salivary gland: where are we. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;S2212-4403(20):30161-30169.

7. Na K, Hernandez-Prera JC, Lim JY, Woo HY, Yoon SO. Characterization of novel genetic alterations in salivary gland secretory carcinoma. Mod Pathol. 2020;33:541-550.

8. Skalova A, Leivo I, Hellquist H, et al. High-grade transformation/dedifferentiation in salivary gland carcinomas: occurrence across subtypes and clinical significance. Adv Anat Pathol. 2021;28:107-118.

9. Network NCC. Head and Neck Cancers (Version 2.2021).

10. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-282.

11. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-739.

12. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020;21:531-540.

13. Skalova A, Michal M, Simpson RH. Newly described salivary gland tumors. Mod Pathol. 2017;30:527-543.

14. Bishop JA. Unmasking MASC: bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head Neck Pathol. 2013;7:35-39.

15. Zheng Z, Liebers M, Zhelyazkova B, et al. Anchored multiplex PCR for targeted next-generation sequencing. Nat Med. 2014;20:1479-1484.

16. Hung YP, Jo VY, Hornick JL. Immunohistochemistry with a pan-TRK antibody distinguishes secretory carcinoma of the salivary gland from acinic cell carcinoma. Histopathology. 2019;75:54-62.

17. Guilmette J, Dias-Santagata D, Nosé V, Lennerz JK, Sadow PM. Novel gene fusions in secretory carcinoma of the salivary glands: enlarging the ETV6 family. Hum Pathol. 2019;83:50-58.

18. Drilon A, Nagasubramanian R, Blake JF, et al. A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. Cancer Discov. 2017;7:963-972.

19. Cocco E, Schram AM, Kulick A, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nat Med. 2019;25:1422-1427.

How to cite this article: Bill R, Deschler DG, Pittet MJ, Pai SI, Sadow PM, Park JC. Diagnostic challenges and successful organ-preserving therapy in a case of secretory carcinoma of minor salivary glands. Cancer Reports. 2022;5(3):e1491. https://doi.org/10.1002/cnr2.1491