Case Report

rare tumors

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A case of metachronous bilateral secretory carcinoma

Jessica Burlile[1], Andrea Collins[2], Joaquin Garcia[3], Kristin Gendron[4], Danielle Cunningham[5] and Robert Foote[5]

Abstract

Secretory carcinoma (SC) was first recognized as a distinct salivary malignancy in 2010. In the nine years since its recognition, there have been multiple reports of SC of the major and minor salivary glands, as well one case of tongue base involvement. Here we present the first reported case of bilateral SC. The first tumor, diagnosed before the recognition of SC, was classified as mucoepidermoid carcinoma. After the contralateral parotid tumor was diagnosed as SC in 2016, the two histologies were compared, and the mucoepidermoid carcinoma was reclassified as SC. In this report, we describe our patient's clinical course and review the SC literature, with a focus on pathologic diagnosis and clinical prognosis.

Keywords

Secretory carcinoma, mammary analogue secretory carcinoma, parotid cancer, bilateral parotid cancer, salivary gland cancer

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Introduction

Cancers of the salivary glands are rare but extremely diverse—the most recent World Health Organization (WHO) Histopathology Classification includes approximately 30 types of benign and malignant tumors.[1] For simplicity, mammary analogue secretory carcinoma has recently been re-classified as "secretory carcinoma" in the WHO 2017 update.[2] There is interest in understanding the clinical course and prognostic features of SC; in particular how it differs from its closest look-alike, acinic cell carcinoma (ACC).[2]

The ETV6-NTRK3 (t(12;15)(p13;25)) fusion gene (shared with breast secretory carcinoma) has proven virtually pathognomonic for SC, with its prevalence estimated between 95% and 98%.[2–4] Although SC and ACC are both generally low-grade in clinicopathologic behavior with relatively favorable prognosis,[5] high-grade cases of SC have been reported, and some small studies have suggested that SC's have higher rates of metastasis and regional lymph node involvement than ACC.[4]

Since the first report of SC, the disease has been increasingly recognized in the literature and in clinical practice.[6] Furthermore, multiple case reports have featured bilateral parotid tumors of benign and malignant etiology.[7] However, to our knowledge, there has never been a reported case of

[1]Transitional Residency, Providence Sacred Heart Medical Center, Spokane, WA, USA
[2]Mayo Clinic Alix School of Medicine, Rochester, MN, USA
[3]Department of Pathology, Mayo Clinic, Rochester, MN, USA
[4]Department of Otolaryngology, Fairview Health System, Woodbury, MN, USA
[5]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA

Corresponding author:
Jessica Burlile, Transitional Residency, Providence Sacred Heart Medical Center, 101 W 8th Avenue, Spokane, WA 99204, USA.
Email: Jessica.burlile@gmail.com

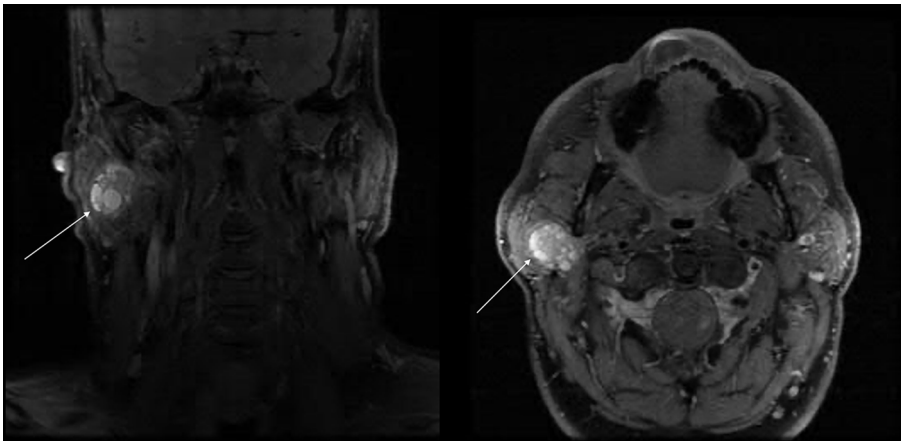


Figure 1. T1, fat suppressed, post-contrast coronal and axial MRI images of the right-sided secretory carcinoma, diagnosed in 2009. Arrows indicate the tumor, which appears to be a complex cystic and solid mass in the deep lobe of the parotid gland, sharply defined relative to the surrounding parotid. No regional adenopathy was noted.

bilateral SC of the parotid glands. Here, we report a case of metachronous SC in which the two tumors appeared approximately seven years apart. It was only after the diagnosis of the patient's second parotid tumor (SC) that the original contralateral histology was re-examined, found to match the second tumor's histology, and reclassified from mucoepidermoid to SC.

Case report

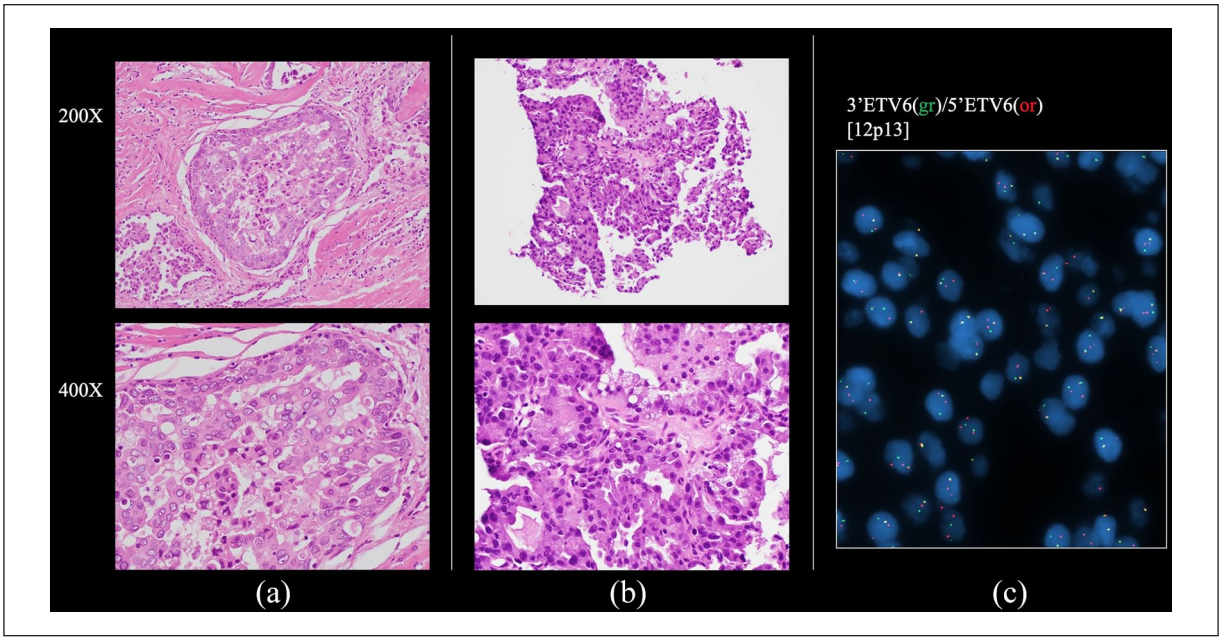
Our patient is a 47-year-old gentleman, never-smoker, who presented with the development of right-sided facial numbness in the setting of an enlarging neck mass, which he noticed approximately 7–8 months prior to initial presentation. He was not experiencing pain, and no lymphadenopathy was noted. A CT scan showed a non-specific mass in the right parotid gland, and MRI confirmed a complex cystic and solid mass in the deep lobe, which appeared sharply defined relative to the surrounding parotid (Figure 1). No regional adenopathy was identified.

Fine needle aspiration of the mass revealed atypical squamous cells in the setting of a cystic lesion, but was largely nondiagnostic. The patient underwent a right-sided parotidectomy with ipsilateral neck dissection of levels I through III. The inferior-most branches of the facial nerve were sacrificed because of adherence to tumor. Pathology of the surgical specimen showed an intermediate grade mucoepidermoid carcinoma, 1.8 cm in greatest dimension, with peripheral cystic changes (Figure 2(a)). The tumor was confined within the parotid gland and margins were negative, although the closest margin was <1 mm from tumor. Pathology did not reveal lymphovascular or perineural invasion, and zero of 31 lymph nodes were positive for tumor. The patient was staged as pT1, pN0, M0.

Post-operative radiotherapy was recommended due to intraoperative findings of suspicious tumor tracking along the facial nerve, close margins, intermediate grade, and invasion into the deep parotid lobe. A dose of 60 Gy was prescribed to be delivered in 30 fractions using intensity modulated radiation therapy. Radiotherapy was delivered to the right parotidectomy tumor bed including the facial nerve in the stylomastoid foramen and facial canal, and level Ib and II cervical lymph nodes on the right.

The patient tolerated treatment well and was followed at regular intervals. Seven years after initial diagnosis and treatment, the patient developed a nontender mass in the left parotid area, accompanied by left ear pain and pressure. Physical exam showed a firm, mobile mass in the left preauricular area adjacent to the tragus and external auditory canal. There was no lymphadenopathy. MRI revealed an enhancing mixed signal in the superficial lobe of the parotid gland: a 1 cm mass with mild exophytic extension into adjacent subcutaneous tissues (Figure 3). Ultrasound revealed a hypoechoic, partially solid, partially cystic nodule in the superficial portion of the left parotid gland. Fine needle aspiration was performed and was non-conclusive, although suspicious for low-grade mucoepidermoid or ACC. Chest X-ray was normal.

The patient underwent a superficial left parotidectomy: the mass was 1.3 cm, superficial, well-encapsulated, and not adherent to the facial nerve. It was completely resected with negative margins (1 mm), and found to be well-differentiated mammary analogue secretory carcinoma. Zero of two lymph nodes were involved by tumor, and no lymphovascular invasion or perineural invasion was identified. The pathology department compared the new slides with the tumor from seven years prior, and found that the histologies were the same (Figure 2(b)). No adjuvant therapy



Figures 2. Representative H&E staining of tumor tissue from (a) 2009 and (b) 2016. As originally described by Skálová et al., pathologic features of SC include a lobulated growth pattern with microcystic and glandular spaces displaying abundant eosinophilic homogenous or bubbly secretory material. Top images 200× magnification, bottom images 400× magnification. (c) FISH from the 2016 tumor tissue indicates ETV6 rearrangement at 12p13. This rearrangement is pathognomonic for secretory carcinoma.

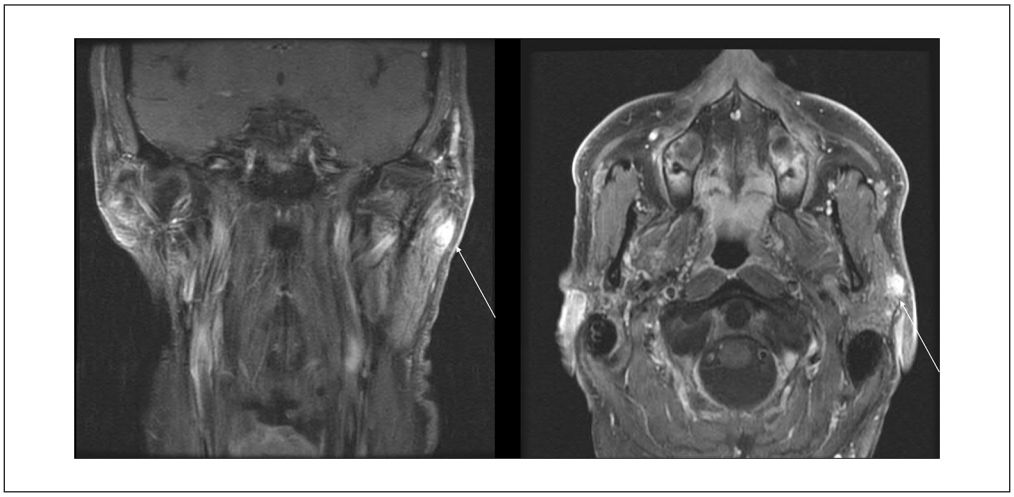


Figure 3. T1, fat suppressed, gadolinium-enhanced coronal and axial MRI images of the left-sided secretory carcinoma, diagnosed in 2015. Arrows indicate the tumor, which is located in the superficial lobe of the parotid gland and appears as an enhancing mixed signal. There is mild exophytic extension into adjacent subcutaneous tissues.

was recommended since the second tumor was low-grade, encapsulated, small, within the superficial lobe, and completely resected. There has been no recurrence of either tumor as of August sixth, 2020.

After the re-classification of the first tumor as SC, tissue from the two tumors was submitted for fluorescence in situ hybridization (FISH) to detect possible *ETV6* rearrangement at 12p13. This rearrangement was present in the 2016 specimen (Figure 2(c)), but unfortunately the 2009 specimen was decalcified and not suitable for FISH. Regardless, histopathology of the 2009 specimen supported the diagnosis of secretory carcinoma (Figure 2(a)).

Discussion

In the United States, there are approximately 2000–2500 malignant salivary gland tumors diagnosed each year, accounting for 5%–8% of all head and neck cancers.[8] The

superficial parotid lobe is the most common location for salivary malignancies, and the disease often presents as a painless swelling without signs of inflammation.[8] Rates of diagnosis are higher in patients who are male and elderly, while women and younger patients seem to have significantly better survival.[8] In contrast, the incidence of SC in particular may be equal between men and women, and the average age at diagnosis is about 46 years.[6] In one analysis, 12% of surveyed cases were pediatric.[6]

The most commonly diagnosed malignant neoplasm of the salivary glands is mucoepidermoid carcinoma.[9,10] In the case presented above, the patient's first parotid mass was diagnosed as mucoepidermoid carcinoma, at a time before the recognition of SC by Skálová et al.[11,12] His tumor's re-classification as SC is not an uncommon occurrence, although little has been written about reclassification from mucoepidermoid carcinoma specifically. Mucoepidermoid carcinoma is composed of mucus-secreting, intermediate, and epidermoid squamous cells in varying proportion. Molecular markers include MUC1 (high-grade), MUC4 (low-grade), t(11;19) translocation, and MAML2 gene rearrangements.[13]

In contrast, Skálová et al.[11] described the histopathology of SC as cells growing in a lobulated growth pattern with microcystic and glandular spaces, displaying eosinophilic homogenous or bubbly secretory material. SC may be positive for MUC1 and MUC4, similar to mucoepidermoid carcinoma, but is also frequently positive for mammaglobin as well as mucicarmine, vimentin, and STAT5a.[11,13] In a seven-year analysis of SC, most cases occurred in the parotid gland (68%) and 98.6% harbored the ETV6-NTRK3 fusion gene.[6] Necrosis was only observed in high-grade histologies, and was otherwise rare.[6]

Characteristics of more aggressive, high-grade SC include strong staining for EGFR and beta-catenin, S-100, and cyclin-D1.[12] The high-grade zone of these cancers displays anaplastic cells in a trabecular pattern, perineural invasion, nuclear polymorphism with distinctive nucleoli, and a lack of secretory activity.[12] It is difficult to obtain microscopically negative margins with high-grade SC, even if macroscopic margins appear clear.[14] Despite the distinct microscopic characteristics of high-grade SC, clinical stage at diagnosis is still thought to be the most powerful predictor of overall prognosis.[12]

The literature is rich with histologic comparisons of ACC and SC, as they closely resemble one another.[5,15] In fact, since the recognition of SC in 2010,[11] pathologists have re-classified many cases of previously diagnosed ACC as SC.[3,16] Globular PAS staining (indicative of mucin production) differentiates SC from ACC, in which staining is more granular.[2] The molecular profiles of the two cancers also differ in that SC stains positive for S100 and mammaglobin and negative for DOG1, while ACC displays opposite characteristics.[2] Most importantly, the ETV6-NTRK3 translocation is not present in cases of ACC.[2] Additionally, SC arises in the minor salivary glands more frequently than ACC, and some authors have suggested that most previously-diagnosed ACC of the minor salivary glands may in fact represent SC.[2,15]

In comparison to ACC, studies suggest that SC tends to present with a significantly higher T stage,[5] concordant with a trend towards worse disease free survival (DFS).[4] In one study of SC, 22% of patients undergoing neck dissection were found to have regional lymph node involvement, three patients had a local recurrence, and one patient died from metastatic disease—demonstrating that SC may be more aggressive than ACC.[4] In the original case series describing SC, 25% of patients experienced local recurrence and 12.5% died of metastatic dissease.[11] Boon et al's recent analysis of 31 patients with SC revealed more encouraging outcomes: only one local recurrence with no regional or distant recurrences.[3] The study found that DFS at 5 and 10 years was 89% at both time points.[3]

Management of SC is challenging because it is a newly recognized disease with minimal data to guide treatment paradigms. Surgery has traditionally been the mainstay of treatment for salivary cancers—previous studies and guidelines suggest improved outcomes with the use of post-operative radiotherapy (PORT) for aggressive histologies, perineural invasion, facial nerve involvement, parotid deep lobe involvement, close or positive margins, lymphovascular invasion, advanced T-classification, and lymph node metastases.[8] Chemotherapy is traditionally recommended only for recurrent and/or metastatic disease.[17] Lymph node metastases in SC were seen more frequently in patients with high-grade histology, advanced T-stage, extracapsular extension, and facial nerve paralysis.[8] In one study evaluating multiple parotid cancer histologies, elective neck irradiation reduced the 10-year nodal metastasis rates from 26% to 0%.[18] SC was not included as it was not recognized at the time of publication, though nodal metastasis for mucoepidermoid carcinoma and ACC were 29% and 0%, respectively.[18]

While reports such as Boon et al.[3] do not advocate for elective neck treatment via dissection or radiotherapy, it is difficult to know if such treatments contributed to the excellent outcomes reported in their series, as 48% of patients received PORT (although radiotherapy targets were reported only about 50% of the time) and 13% underwent neck dissection. The one local recurrence in this study did not receive PORT.[3] In the seven-year analysis of SC, 20% of surveyed cases were treated with adjuvant chemotherapy, radiotherapy, or both.[6] Combined with the previously reported higher incidence of nodal spread and locoregional failure for SC versus ACC, it appears that SC may be more similar to mucoepidermoid carcinoma than ACC regarding locoregional spread and overall aggressiveness.

The etiology of our patient's contralateral SC remains an enigma. The possibility that radiotherapy treatment predisposed the contralateral parotid gland to developing a

second cancer seems very unlikely, as examination of the radiotherapy plan reveals that the contralateral parotid gland received a mean dose of 4.2 Gy (maximum 7 Gy).[19] The patient did not undergo any genetic testing. Literature in the area of salivary malignancy genomics is sparse, but an association between BRCA gene mutations and salivary cancer has been described.[20,21] Given SC's similarity to secretory carcinoma of the breast, this association may warrant further investigation.

Conclusion

The prevalence of SC of the parotid gland is likely underestimated given that it is a newly recognized histology. It is likely that upon re-examination of specimens of similar histology, such as ACC, the prevalence of SC would be higher than currently reported. The phenotype of SC ranges from relatively indolent to aggressive disseminated disease, with several cases of death having been reported. Taken together, it appears prudent to treat SC similarly to other parotid malignancies, with the addition of PORT for high-risk features. The incidence of synchronous or metachronous bilateral SC appears to be rare as this patient's case represents the first reported bilateral secretory carcinoma.

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Author contributions

JB wrote the first draft of the manuscript and made final revisions. AC and JG communicated with outside hospitals and obtained pathologic information critical for the completion of the case report. RF oversaw the care of this patient, provided guidance with the preparation of each draft, and aided in obtaining images. DC assisted with revisions, submission, and ethics. All authors including KG reviewed, edited, and approved the final version of the manuscript.

Conflict of interest

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Ethical approval

IRB exemption was obtained to report this case.

Informed consent

Written informed consent was obtained from the patient for their anonymised information to be published in this article.

ORCID iD

Jessica Burlile https://orcid.org/0000-0001-8653-1045

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