Diagnosis and treatment of secretory carcinoma arising from the oral minor salivary gland

Two case reports

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Abstract

Introduction: Secretory carcinoma (SC) is a malignancy of the salivary glands, which is similar to SC of the breast regarding its association with neurotrophic tyrosine receptor kinase fusion-positive gene. SC is a recently described salivary gland tumor, and there are a few reports describing oral minor salivary gland-derived SC. We reported two cases of SC in the oral cavity and reviewed the literature.

Patient concerns: The patients included a 65-year-old Japanese woman who presented with a mass of the upper lip and an 84-year-old Japanese man who presented with a mass on the buccal mucosa.

Diagnosis: Diagnosis was based on histomorphological and immunohistochemical findings and identification of a specific translocation of the ETS variant 6-neurotrophic receptor tyrosine kinase 3 gene fusion. Case 1 was finally diagnosed using reverse transcription-polymerase chain reaction with formalin-fixed paraffin-embedded tissue samples, while case 2 was diagnosed using fluorescence in situ hybridization analysis.

Interventions and outcomes: In case 1, excisional biopsy was done and there was no recurrence observed in five-year follow-up. In case 2, tumor resection was done and there was no recurrence observed in two-year follow-up.

Conclusion: It is highly likely for many cases of SC to be initially diagnosed as acinic cell carcinoma (AciCC) owing to their similar histological findings. The treatment strategy for minor salivary gland-originated SC is similar to that of AciCC; however, SC is often highly malignant and involves a high risk of cervical lymph node metastasis. Thus, establishing an accurate diagnosis together with pathologists and confirming the presence of the ETS variant 6-neurotrophic receptor tyrosine kinase 3 fusion gene using genetic analysis is important.

Abbreviations: AciCC = acinic cell carcinoma, CK19 = cytokeratin 19, ETV6-NTRK3 = ETS variant 6-neurotrophic receptor tyrosine kinase 3, NTRK = neurotrophic tyrosine receptor kinase, SC = secretory carcinoma.

Keywords: ETS variant 6-neurotrophic receptor tyrosine kinase 3 fusion gene, mammary analogue secretory carcinoma, oral cavity, secretory carcinoma.

1. Introduction

In 1996, McDivitt et al reported mammary secretory carcinoma (SC) as a histological subtype of breast cancer.[1] Mammary SC is caused by the ETS variant 6-neurotrophic receptor tyrosine kinase 3 (ETV6-NTRK3) fusion gene through the phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase pathways.[2] In 2002, Hirokawa et al noted histological similarities between acinic cell carcinoma (AciCC) of the salivary gland and mammary SC.[3] In 2010, Skálová et al found that the ETV6-NTRK3 fusion gene was expressed in salivary gland tumors that were previously diagnosed as AciCC and proposed the name mammary analogue SC.[4] However, in 2017, the
WHO classification of head and neck tumors described it as SC of the salivary gland; hence, the name was unified to SC in this report.

SC in the head and neck region develops in individuals in their 40s, which is a relatively early age of onset compared to that for AciCC; however, a childhood-onset case has similarly been reported. SC showed no sex predilection. Approximately 60–70% of the cases were located in the parotid gland, and the total number of cases in the major salivary glands, including the submandibular gland, accounted for approximately 70–80%. Overall, there are a few reports describing minor salivary gland-derived SC. The true frequency of occurrence is unclear because SC is a recently described disease entity, and a few SC cases could have been previously diagnosed as AciCC. Although most SCs are low-grade malignancies, a small subset is reported to be high-grade compared to AciCC. Most SCs are low-grade malignancies, a small subset is reported to be high-grade compared to AciCC,

We reported two cases of SC in the oral cavity and discussed the grade of malignancy of SC with pooled analysis of the recent literature.

2. Case presentation

2.1. Case 1

A 65-year-old Japanese woman with a two-year history of a gradually enlarging mass on the left side of the upper lip consulted with the Department of Oral and Maxillofacial Surgery, Gunma University Hospital. On clinical examination, a painless, elastic-hard, protruding mass measuring 15 x 10 mm was noted on the left side of the upper lip (Fig. 1A). The overlying mucosa was a flat surface, and the color was normal with no adhesion to the mass. The mass exhibited moderate intensity on contrast T1-weighted magnetic resonance imaging (MRI) and high intensity on short T1 inversion recovery. Additionally, the continuity of the orbicularis oris muscle was retained (Fig. 1B, C). On fluorodeoxyglucose-positron emission tomography, no abnormal accumulation was noted in the cervical lymph nodes or distant organs. These clinical and MRI findings suggested a benign salivary gland tumor. An excisional biopsy was performed, and as the mass was not adherent to the surrounding tissues, dissection was easily performed. Macroscopic observation of the cut surface of the excisional biopsy specimen revealed that the mass was spherical and solid, and the boundary with the overlying mucosa was clear. Histopathological examination revealed that the mass was a 15-mm nodular tumor, and its boundary with the surrounding tissue was clear with no evidence of encapsulation (Fig. 2A). It showed mixed characteristics of microcystic (Fig. 2B), papillary-cystic (Fig. 2C), and follicular (Fig. 2D) patterns of tumor cell proliferation. Polymorphous low-grade adenocarcinoma, AciCC, and SC were considered in the differential diagnosis based on the results of hematoxylin and eosin staining; immunostaining and special staining were performed for differentiation (Table 1).
Figure 2. Histological findings (hematoxylin and eosin staining). The lesion was a nodular tumor, and the boundary with the surrounding area was clear, with no evidence of encapsulation (A) (magnification 10×). Microcystic (B) (magnification 200×), papillary-cystic (C) (magnification 200×), and follicular (D) (magnification 400×) patterns of tumor cell proliferation were mixed.

| Antibodies used for immunohistochemical study. |
|-----------------------------------------------|
| **Primary antibodies** | **Source** | **Dilution** | **Clone** | **Purpose** |
|-------------------------|------------|--------------|-----------|-------------|
| CK19                    | Novostra   | 1:100        | Mouse monoclonal | • Epithelial cell marker  
|                         |            |              |           | • Develops in some basal cells, staining pattern that is homogenous for the breast malignant tumor  
|                         |            |              |           | • Mesenchymal cell marker  
|                         |            |              |           | • Intermediate filament which is common to a mesenchyma system cell  
| S-100                   | Dako       | 1:200        | Mouse monoclonal | • Intermediate filament which is common to a mesenchyma system cell  
|                         |            |              |           | • Breast cancer specific marker  
|                         |            |              |           | • Develops in breast duct epithelium, an apocrine gland and an eccrine gland epithelium of the normal skin  
| Vimentin                | Dako       | 1:10         | Mouse monoclonal | • Breast cancer specific markers  
|                         |            |              |           | • Develops in breast duct epithelium, an apocrine gland of the normal skin  
| Mammaglobin             | Dako       | 1:100        | Mouse monoclonal | • Breast cancer specific markers  
|                         |            |              |           | • GATA family which is the transcription factor in the nucleus  
|                         |            |              |           | • Expression abnormal for breast cancer, colon cancer  
| GCDGP15                 | Abcam      | 1:200        | Mouse monoclonal | • Membrane-bound mucin  
|                         |            |              |           | • Participate in cell proliferation through the mutual participation with the glycoproteinErb2/HER2 family  
|                         |            |              |           | • Expression abnormal for breast cancer, pancreatic cancer, cholangiocarcinoma, colon cancer  
| MUC4                    | Abcam      | 1:500        | Mouse monoclonal | • Membrane-bound mucin  
|                         |            |              |           | • Participate in cell proliferation through the mutual participation with the glycoproteinErb2/HER2 family  
|                         |            |              |           | • Expression abnormal for breast cancer, pancreatic cancer, cholangiocarcinoma, colon cancer  

CK19 = cytokeratin 19, GCDGP15 = Gross cystic disease fluid protein 15.
Immunohistochemistry showed that the tumor was positive for cytokeratin 19 (CK19), S-100, vimentin, mammaglobin, gross cystic disease fluid protein 15 (GCDFP15), and GATA3. These findings are consistent with the immunostaining findings frequently observed in SC.\[4,13–16\] The MIB-1 index, which indicates tumor cell proliferative activity, was 3% (Fig. 3A-H). In addition, there were a few periodic acid–Schiff-positive granules in the cytoplasm of tumor cells (Fig. 4A). Periodic acid–Schiff with diastase digestion staining was positive in the abundant eosinophilic homogeneous secretions in microcystic and follicular spaces (Fig. 4B). Furthermore, the examination for ETV6-NTRK3 gene fusion was performed using a formalin-fixed paraffin-embedded tissue sample, and a positive result was obtained in reverse transcription-polymerase chain reaction (Fig. 5A). Direct sequencing of the amplified reverse transcription-polymerase chain reaction product confirmed the presence of ETV6-NTRK3 rearrangement (Fig. 5B), leading to the definitive diagnosis of SC. To ensure a malignant negative margin, additional resection was performed under general anesthesia, and the resection margin was set at 10mm from the scar of the previous excisional biopsy. No residual tumor tissue was observed in the resected specimen. The tumor was staged pT1 cN0, and adjuvant therapy was not indicated. For five years postoperatively, the patient showed no evidence of recurrence or metastasis.

### 2.2. Case 2

An 84-year-old Japanese man presenting with a mass on the left buccal mucosa consulted with the Department of Oral and Maxillofacial Surgery, Gunma University Hospital. On clinical examination, an elastic-hard mass measuring 17 × 15 mm was observed on the left buccal mucosa (Fig. 6A). The mass exhibited moderate intensity on contrast T1-weighted MRI, and advancement to the buccinator muscle was noted (Fig. 6B). The fluorodeoxyglucose-positron emission tomography scan revealed that the maximum standardized uptake value (SUVmax) of FDG was 4.6 in the left buccal mucosa (Fig. 6C). There was no evidence of metastasis in the cervical lymph nodes or distant organs. In the biopsy specimen, microcystic and papillary-cystic patterns of tumor cells that were suggestive of AciCC or SC were observed. These clinical, histological, and MRI findings sug-
gested a malignant left buccal mucosal salivary gland tumor. Tumor resection with a 10-mm safety margin was performed under general anesthesia. Macroscopic observation of the cut surface of the surgical specimen revealed that it was white and solid, and the boundary with the surrounding tissues was clear. Histopathological examination showed that it was a 15-mm nodular tumor, and its boundary with the surrounding tissues was clear, with no evidence of encapsulation (Fig. 7A). Furthermore, it showed mixed features of microcystic and papillary-cystic patterns of tumor cell proliferation (Fig. 7B,C).

Immunohistochemistry showed that the tumor was positive for CK19, S-100, vimentin, mammagloblin, GCDFP15, and MUC4. These findings are consistent with the immunostaining findings, which are frequently observed in SC (Fig. 8A-I). The MIB-1 index was 10%. In addition, genetic analysis was performed using fluorescence in situ hybridization analysis, wherein the ETV6-NTRK3 fusion gene accompanied by chromosomal translocation t(12; 15)(p13; q25) was detected (Fig. 9A-D). Based on these findings, a definitive diagnosis of SC was established. The tumor was staged pT1 cN0, and adjuvant

Figure 4. Special staining findings. There were a few periodic acid-Schiff (PAS)-positive granules in the tumor cell cytoplasm (A) (magnification 400×). Diastase digestion PAS staining was positive in abundant eosinophilic homogeneous secretions in microcystic and follicular spaces (B) (magnification 400×).

Figure 5. Reverse transcription-polymerase chain reaction (RT-PCR) for the detection of ETV6-NTRK3 fusion gene transcripts. RT-PCR analysis showed amplification of the ETV6-NTRK3 fusion gene (A). Direct sequencing of the amplified RT-PCR product confirmed the presence of ETV6-NTRK3 rearrangement (B).
therapy was not indicated. At two years after surgery, the patient had a good prognosis with no recurrence or metastasis.

3. Discussion

Sixty-eight cases of minor salivary gland-originated SC have been reported between 2010 and 2017. These cases were identified in a literature search conducted using keywords such as “mammary analogue secretory carcinoma,” “secretory carcinoma,” “oral cavity,” “buccal mucosa,” “lip,” “palate,” “gingiva,” and “tongue” in PubMed and the Japan Medical Abstracts Society databases. Age, sex, location in the oral cavity, size, TNM classification, treatment, metastasis, local recurrence, follow-up period, and survival rate were all described in 21 of the 68 cases. Pooled analysis of 23 cases, which included the two patients of the present case report, was performed (Table 2). Of the 23 patients, SC developed in the lips in nine patients and the buccal mucosa in seven patients, including our patients. These two locations accounted for 70% of all cases. As the labial mucosa is classified as buccal mucosa in the oral cavity category of Union for International Cancer Control classification, the buccal mucosa accounts for approximately 70% of all cases. Histopathologically, tumor cells in SC proliferate in microcystic, papillary-cystic, and follicular patterns. However, as this histological morphology is similar to that of AciCC, differentiation between SC and AciCC is difficult using HE staining alone. Bishop et al reported that 19% of parotid gland AciCC cases were SC. Similarly, nine of the 23 cases with oral minor salivary gland-originated SC were initially diagnosed as AciCC, suggesting that the differentiation between SC and AciCC is difficult. In our cases, immunostaining revealed that the tumor was positive for CK19, S-100, vimentin, mammaglobin, GCDFP15, GATA3, and MUC4. These markers have been reported to be useful for differentiating SC from other salivary gland tumors. The results were consistent with the findings frequently observed in the previously reported cases of SC, thereby facilitating differentiation (Tables 1 and 3). However, these immunohistochemical findings are not uniform in all SC and AciCC cases; therefore, it is essential to confirm the presence of the ETV6-NTRK3 fusion gene by genetic analysis to establish a definite diagnosis. Thus, an accurate diagnosis of SC can be established by the sequential use of hematoxylin and eosin histological screening followed by immunohistological investigation and genetic analysis. Surgical resection was performed as the initial treatment in all 23 patients. Local recurrence was noted in three cases, which may have been due to surgical margin positivity in two cases and a close margin in one case. As the histopathological findings of excisional biopsy revealed a close

Figure 6. Clinical findings. An elastic-hard mass measuring 17 × 15 mm in size was observed on the left buccal mucosa (A). The mass exhibited moderate intensity on contrast T1-weighted magnetic resonance imaging, and advancement to the buccinator muscle was noted (B). On fluorodeoxyglucose-positron emission tomography (FDG-PET) with an SUVmax of 4.6, FDG accumulation was detected in the left buccal mucosa (C).
margin in case 1, additional resection was performed with a 10-mm safety margin to prevent local recurrence. Although most SC is considered a low-grade malignancy, additional resection should be performed to secure a safety surgical margin in positive cases and cases with a margin close to the tumor to prevent local recurrence. Seventeen of the 23 cases with oral minor salivary gland-originated SC were treated at cT1N0, that is, in the early stage. Late cervical lymph node metastasis to cervical lymph nodes developed in three cases (14.3%) and seven years after surgery in one case. The frequency of cervical lymph node metastasis is higher in SC than in AciCC: 8–11% in AciCC and approximately 25% in SC. Sethi et al reported that many cases of intercalated duct-type cell-predominant AciCC are metastatic, and these are highly likely to be SC, thereby confirming that the frequency of cervical metastasis may be higher in SC than in AciCC. Therefore, long-term postoperative observation may be necessary for SC cases considering the possibility of late cervical lymph nodes metastasis. In general, most SCs are considered low-grade malignancies, and the treatment outcome is favorable. This was supported by the fact that all 23 patients with oral minor salivary gland-originated SC survived for four months to nine years. However, a few patients with parotid gland-originated SC developed distant metastasis and died, suggesting a slightly poor outcome, and cases of high-grade transformation containing a highly malignant tumor component with poor outcomes have similarly been reported. Furthermore, the possibility of differences in the disease-free survival time among AciCC cases has been previously suggested. Therefore, differentiation between the two carcinoma types is important. To evaluate true malignancy and treatment outcomes of oral minor salivary gland-originated SC and AciCC, re-investigation of the previous cases diagnosed as AciCC may be necessary. SC is considered an NTRK fusion-positive cancer, together with SC of the breast and infantile fibrosarcoma. When the normal NTRK gene is fused with another gene to form an NTRK fusion gene, the tropomyosin receptor kinase (TRK) fusion protein is produced, which continuously activates the phosphoinositide phospholipase Cγ, Mitogen-activated protein kinase, and PI3K signal transmission pathways and promotes cancer cell proliferation. More recently, Skalova et al reported VIM-RET gene fusion in SC, and this finding may further expand the molecular definition of SC.

Entrectinib is a potent inhibitor of TRK A, B, and C, which has been shown to elicit anti-tumor activity against NTRK gene fusion-positive solid tumors, including SC. The effectiveness of entrectinib was recently demonstrated in the studies of tumor alterations responsive to targeting receptor kinases-2 involving patients with NTRK fusion-positive cancer; five of the six patients with SC equally responded to the treatment. Entrectinib inhibits the phosphorylation of the TRK fusion protein, which in turn inhibits its downstream signal transmission and consequently results in the inhibition of cancer cell proliferation. Thus, it may be a useful treatment option for patients in whom surgery is not indicated and those with distant metastases.

Figure 7. Histological findings (hematoxylin and eosin staining). The lesion was a nodular tumor, and the boundary with the surrounding area was clear, with no evidence of encapsulation (A) (magnification 10×). Microcystic (B) (magnification 400×) and papillary-cystic (C) (magnification 200×) patterns of tumor cell proliferation were mixed.
Figure 8. Immunohistochemical findings. Hematoxylin and eosin (A,B) (magnification 10×, 200×) and immunostaining with Cytokeratin 19 (C), S-100 (D), Vimentin (E), Mammaglobin (F), gross cystic disease fluid protein 15 (G), and MUC4 (H) (magnification 200×). An index of tumor cell proliferative activity, the MIB-1 index, was 10% (I) (magnification 200×).

Table 2

| Patient no. | Author (year) | Age | Sex | Location | Size (mm) | Stage at time of Diagnosis | Surgical Margins | Metastasis (y, mo) | Local Recurrence (y, mo) | Treatment | Follow-up (y, mo) | Outcome |
|-------------|---------------|-----|-----|----------|-----------|--------------------------|------------------|-------------------|------------------------|------------|------------------|---------|
| 1           | Skalova et al. 2010 [4] | 51 F | Buccal mucosa | 10 | T1N0M0 | NA | No | No | Excision | 4 yr | NED |
| 2           | Skalova et al. 2010 [4] | 32 M | Upper lip | 10 | T1N0M0 | NA | LN 2 yr | 2 mo | Excision, re-excision ND+RT for LN metastasis | 9 yr, 5 mo | NED |
| 3           | 48 M | Soft palate | 15 | T1N0M0 | NA | No | No | Excision | 6 yr | NED |
| 4           | Kratochvil et al. 2012 [7] | 48 F | Upper lip | 10 | T1N0M0 | NA | No | No | Excision | 8 mo | NED |
| 5           | 52 M | Lower lip | 7 | T1N0M0 | NA | No | No | Excision | 4 mo | NED |
| 6           | Griffith et al. 2013 [14] | 51 M | Buccal mucosa | 21 | T2N0M0 | NA | No | No | Excision | 4 mo | NED |
| 7           | Laco et al. 2013 [14] | 34 F | Upper lip | 15 | T1N0M0 | Negative | No | No | Excision | 1 yr, 3 mo | NED |
| 8           | Luo et al. 2014 [9] | 41 F | Hard palate | 4 | T1N2M0 | NA | No | No | Excision, ND+RT | 10 mo | NED |
| 9           | Helkamaa T et al. 2015 [24] | 55 M | Hard palate | 20 | T2N0M0 | Negative | No | No | Excision | 1 yr, 6 mo | NED |
| 10          | Aizawa et al. 2015 [21] | 41 M | Lower lip | 15 | T1N0M0 | NA | LN 2yr | No | Excision, ND (for LN metastasis) | 6 yr | NED |
| 11          | Majewska et al. 2015 [21] | 54 M | Hard palate | 20 | T1N0M0 | Close | LN 4yr | Recurrence (4y) | Excision-re-excision, SND,RT for local recurrence and LN metastasis | 12 yr, 7 mo | NED |
| 12          | Skalova et al. 2016 [22] | 48 M | Upper lip | 10 | T1N0M0 | Positive | No | No | Excision, re-excision for local recurrence | 9 mo | NED |
| 13          | 69 F | Retromolar gingiva | 6 | T1N0M0 | Negative | No | No | Excision | 2 yr | NED |
| 14          | 31 F | Buccal mucosa | 10 | T1N0M0 | Negative | No | No | Excision | 11 mo | NED |

(continued)
Figure 9. ETV6-NTRK3 fluorescence in situ hybridisation. Signals of the ETV6 and NTRK3 probes are presented in green and red, respectively. The number of fusion gene signals was classified into four patterns: 1 fusion gene signal (A), 2 signals (B), 3 signals (C), and 4 signals (D).

Table 2 (continued).

| Patient no. | Author (year) | Age | Sex | Location     | Size (mm) | Stage at time of Diagnosis | Surgical Margins | Metastasis (yr, mo) | Local Recurrence (yr, mo) | Treatment                                    | Follow-up (yr, mo) | Outcome |
|-------------|---------------|-----|-----|--------------|-----------|----------------------------|------------------|---------------------|----------------------------|---------------------------------------------|-------------------|---------|
| 15          |               | 24  | F   | Buccal mucosa| 10        | T1N1M0                     | Positive         | LN                  | 2yr                        | Excision                      | 2 yr, 4 mo       | RD      |
| 16          |               | 62  | F   | Lip          | 10        | T1NOm0                     | Negative         | No                  | No                         | Excision                      | 3 yr              | NED     |
| 17          | Hindocha et al. 2017[23] | 27  | F   | Upper lip    | 24        | T1N0M0                     | Positive         | No                  | No                         | Excision re-excision for positive margin | 9 mo              | NED     |
| 18          | Bissinger et al. 2017[24] | 34  | M   | Oral floor   | 8         | T1N0M0                     | NA               | No                  | No                         | Excision, ND                  | 2 yr, 4 mo       | NED     |
| 19          | Kai et al. 2017[25]    | 58  | M   | Buccal mucosa| 30        | T2N0M0                     | NA               | No                  | No                         | Excision                      | 1 yr              | NED     |
| 20          | Bolere et al. 2019[26] | 57  | M   | Hard palate  | 20        | T2N0M0                     | Negative         | No                  | No                         | Excision, ND                  | 3 yr              | NED     |
| 21          | Pasdel et al. 2019[8]  | 54  | F   | Buccal mucosa| 10        | T1N0M0                     | NA               | No                  | No                         | Excision                      | 2 mo              | NED     |
| 22          | Present case.1     | 65  | F   | Upper lip    | 15         | T1N0M0                     | Close            | No                  | No                         | Excision, re-excision for close margin | 5 yr              | NED     |
| 23          | Present case.2     | 84  | M   | Buccal mucosa| 17        | T1N0M0                     | Negative         | No                  | No                         | Excision                      | 2 yr              | NED     |

LN = lymph node, NA = not available, ND = neck dissection, NED = no evidence of disease, RD = residual disease, RT = radiation therapy, SND = selective neck dissection.
Table 3

| IHC Marker | SC, (%)  | AciCC, (%) |
|------------|----------|------------|
| CK19 (+)   | 15/15 (100) | 2/10 (20) |
| S-100 protein (+) | 15/15 (100) | 4/12 (33) |
| Vimentin (+) | 15/15 (100) | 3/12 (25) |
| Mammmaglobin (+) | 22/25 (88) | 1/19 (5) |
| GCDFP-15 (+) | 8/11 (73) | 4/10 (40) |
| MUC4 (+) | 9/11 (82) | 0/8 (0) |

CK19 = cytokeratin 19.

4. Conclusion

We reported two patients with oral cavity-originated SC and performed a pooled analysis of previously reported SC cases. It is highly likely that many cases of SC were previously diagnosed as AciCC owing to their similar histological findings. The treatment strategy for minor salivary gland-originated SC is similar to that for AciCC; however, SC is often highly malignant, resulting in a high risk of cervical lymph node metastasis. According to these results, establishing an accurate diagnosis together with pathologists and confirming the ETV6-NTRK3 fusion gene by genetic analysis is important.

Acknowledgments

The author would like to thank Editage (www.editage.com) for English language editing.

Author contributions

MO contributed to the conception and design, acquisition of data, analysis, and interpretation of data. TY, KS, TS, JH and TM contributed to analysis of the patient’s data/findings. MS carried out the immunoassays and immunohistochemical staining. SY conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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References

[1] McDvitt RW, Stewart FW. Breast carcinoma in children. JAMA 1966;195:388–90.
[2] Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer cell 2002;2:367–76.
[3] Hirokawa M, Sugihara K, Sai T, et al. Secretory carcinoma of the breast: a tumour analogous to salivary gland acinic cell carcinoma? Histopathology 2002;40:223–9.
[4] Skalová A, Vaneeck T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a histopathologic undescribed salivary gland tumor entity. Am J Surg Pathol 2010;34:599–608.
[5] El-Naggar AK, Chan JKC, Takata T, et al. The fourth edition of the head and neck World Health Organization blue book: editors’ perspectives. Ham Pathol 2017;66:10–2.
[6] Sethi R, Kozin E, Remenschneider A, et al. Mammary analogue secretory carcinoma: update on a new diagnosis of salivary gland malignancy. Laryngoscope 2014;124:188–95.
[7] Bishop JA. Unmasking MASK: bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head and Neck Pathol 2013;7:35–9.
[8] 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;2019:3841650.
[9] Luo W, Lindley SW, Lindley PH, et al. Mammary analogue secretory carcinoma of salivary gland with high-grade histology arising in hard palate, report of a case and review of literature. Int J Clin Exp Pathol 2014;7:9008–22.
[10] Aizawa T, Okui T, Kitagawa K, et al. A case of mammary analogue secretory carcinoma of the lower lip. J Oral Maxilofac Surg Med Pathol 2016;28:777–82.
[11] Chosea S, Griffith C, Assaad A, et al. Clinicopathological characterization of mammary analogue secretory carcinoma of salivary glands. Histopathology 2012;61:387–94.
[12] Skalová A, Vaneeck T, Majewska H, et al. Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, β-catenin, EGFR, and CCND1 genes. Am J Surg Pathol 2014;38:23–33.
[13] Mariano FV, dos Santos HT, Azañero WD, et al. Mammary analogue secretory carcinoma of salivary glands is a lipid-rich tumour, and adipophilin can be valuable in its identification. Histopathology 2013; 63:538–67.
[14] Jung MJ, Song JS, Kim SY, et al. Finding and characterizing mammary analogue secretory carcinoma of the salivary gland. Korean J Pathol 2014;47:36–43.
[15] Chênever T, Duvvuri U, Chosea S, et al. DOG1: a novel marker of salivary acinar and intercalated duct differentiation. Mod Pathol 2012;25:919–29.
[16] Andrade E, Teixeira L, Montalli V, et al. Epithelial membrane antigen and DOG1 expression in minor salivary gland tumors. Am J Surg Pathol 2019;43:151408.
[17] Khurram SA, Sultan-Khan J, Atkey N, et al. Cytogenetic and immunohistochemical characterization of mammary analogue secretory carcinoma of salivary glands. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:731–42.
[18] Krzitchvil FJJIII, Stewart JC, Moore SR. Mammary analogue secretory carcinoma of salivary glands: a report of 2 cases in the lips. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:630–5.
[19] Griffith CC, Stelow EB, Saqui A, et al. The cytological features of mammary analogue secretory carcinoma: a series of 6 molecularly confirmed cases. Cancer Cytopathol 2013;121:234–41.
[20] Laco J, Svađler MJ, Andrejs J, et al. Mammary analogue secretory carcinoma of salivary glands: a report of 2 cases with expression of basal/myoepithelial markers (calponin, CD10 and p63 protein). Pathol Res Pract 2013;209:167–72.
[21] Helkamaa T, Rossi S, Mesimäki K, et al. Mammary analogue secretory carcinoma of minor palatal salivary glands: A case report and review of the literature 2015;27:698–702.
[22] Majewska H, Skalova A, Stodulski D, et al. Mammary analogue secretory carcinoma of salivary glands: a new entity associated with ETV6 gene rearrangement. Virchows Arch 2015;466:245–54.
[23] Skalová A, Vaneeck T, Simpson RH, et al. Mammary analogue secretory carcinoma of salivary glands: molecular analysis of 25 ETV6 gene rearranged tumors with lack of detection of classical ETV6-NTRK3 fusion transcript by standard RT-PCR: report of 4 cases harboring etv6-x gene fusion. Am J Surg Pathol 2016;40:3–13.
[24] Hindoche N, Wilson MH, Pring M, et al. Mammary analogue secretory carcinoma of the salivary glands: a diagnostic dilemma. Br J Oral Maxillofac Surg 2017;55:290–2.
[25] Bissinger O, Götz C, Kolk A, et al. Mammary analogue secretory carcinoma of salivary glands: diagnostic pitfalls with distinct immunohistochemical profile and molecular features. Rare Tumors 2017;9:1762.
[26] Kai K, Minesaki A, Suzuki K, et al. Difficulty in the cytodiagnosis of mammary analogue secretory carcinoma: survey of 109 cytologists with a case originating from a minor salivary gland. Acta Cytologica 2017;61:469–76.
[27] Bollier C, Murphy J, Qaisi M, et al. Mammary analogue secretory carcinoma of the palate: Case report and review of the literature. Case Rep Dent 2019;7:416302.
[28] Griffith C, Seethala R, Chiosea SI. Mammary analogue secretory carcinoma: a new twist to the diagnostic dilemma of zymogen granule poor acinic cell carcinoma. Virchows Arch 2011;459:117–8.
Abe M, Inaki R, Kanno Y, et al. Molecular analysis of a mammary analog secretory carcinoma in the upper lip: novel search for genetic and epigenetic abnormalities in MASC. Int J Surg Case Rep 2015;9:8–11.

Connor A, Perez-Ordoñez B, Shago M, et al. Mammary analog secretory carcinoma of salivary gland origin with the ETV6 gene rearrangement by FISH: expanded morphologic and immunohistochemical spectrum of a recently described entity. Am J Surg Pathol 2012;36:27–34.

Ito Y, Ishibashi K, Masaki A, et al. Mammary analogue secretory carcinoma of salivary glands: a clinicopathologic and molecular study including 2 cases harboring ETV6-X fusion. Am J Surg Pathol 2015;39:602–10.

Keisling M, Bianchi M, Pascasio JM. Mammary analog secretory carcinoma of salivary gland in a 5 year old: case report. Int J Ped Otorhinolaryngol Extra 2014;9:163–5.

Serrano-Arevalo ML, Mosqueda-Taylor A, Domínguez-Malagon H, Michal M. Mammary analogue secretory carcinoma (MASC) of salivary gland in four Mexican patients. Med Oral Patol Oral Cir Bucal 2015;20:e23–9.

Stevens TM, Kovalovsky AO, Velosa C, et al. Mammary analog secretory carcinoma, low-grade salivary duct carcinoma, and mimickers: a comparative study. Mod Pathol 2015;28:1084–100.

Din NU, Fatima S, Kayani N. Mammary analogue secretory carcinoma of salivary glands: a clinicopathologic study of 11 cases. Ann Diag Pathol 2016;22:49–53.

Zardawi IM, Hook P. Mammary analogue secretory carcinoma of minor salivary glands. Pathology 2014;46:667–9.

Guilmette J, Nielsen GP, Faquin WC, et al. Ultrastructural characterization of mammary analogue secretory carcinoma of the salivary glands: a distinct entity from acinic cell carcinoma? Head Neck Pathol 2017;11:419–26.

Khurram SA, Sultan-Khan J, Atkey N, Speight PM. Cytogenetic and immunohistochemical characterization of mammary analogue secretory carcinoma of salivary glands. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:731–42.

Roy S, Saluja K, Zhu H, Zhao B. Mammary analogue secretory carcinoma of minor salivary glands: a rare case series and review of the literature. Ann Clin Lab Sci 2018;48:94–9.

Urano M, Nagao T, Miyabe S, et al. Characterization of mammary analogue secretory carcinoma of the salivary gland: discrimination from its mimics by the presence of the ETV6-NTRK3 translocation and novel surrogate markers. Human Pathology 2015;46:94–103.

Fehr A, Lönig T, Stenman G. Mammary analogue secretory carcinoma of the salivary glands with ETV6-NTRK3 gene fusion. Am J Surg Pathol 2011;35:1600–2.

Guilmette J, Nielsen GP, Faquin WC, et al. Ultrastructural characterization of mammary analogue secretory carcinoma of the salivary glands: a distinct entity from acinic cell carcinoma? Head Neck Pathol 2017;11:419–26.

Venkat S, Fitzpatrick S, Drew PA, et al. Secretory Carcinoma of the Oral Cavity: A Retrospective Case Series with Review of Literature. Head Neck Pathol 2021;15:893–904.

Neville BW, Damm DD, Allen CM. Oral and maxillofacial pathology. 4th ed. 2016; An Imprint of Elsevier, 457–549.

Chiosea SI, Griffith C, Assaad A, Seethala RR. The profile of acinic cell carcinoma after recognition of mammary analog secretory carcinoma. Am J Surg Pathol 2012;36:343–50.

Shah AA, Wenig BM, LeGallo RD, et al. Morphology in conjunction with immunohistochemistry is sufficient for the diagnosis of mammary analogue secretory carcinoma. Head Neck Pathol 2015;9:85–95.

Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018;15:731–47.

Vaishnavi A, Le AT, Doebbe RC, et al. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov 2015;5:25–34.

Skálová A, Banečkova 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;44:1295–307.

Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res 2018;24:5807–14.

Rolfo C, Ruiz R, Giovannetti E, et al. Entrectinib: a potent new TRK, ROS1, and ALK inhibitor. Expert Opin Investig Drugs 2015;24:1493–500.