Macrocystic secretory carcinoma arising from the buccal minor salivary gland clinically mimicking a mucocele: A case report

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Abstract. Secretory carcinoma (SC) is an uncommon salivary gland tumor that has been recently conceptualized. The present report describes a case of SC that was diagnosed as a mucocele on preoperative examination. A 46-year-old man presented to the Department of Oral and Maxillofacial Surgery at Saiseikai Senri Hospital (Suita-shi, Japan) with a main complaint of swelling of the right buccal mucosa. A mobile, elastic, hard mass was found beneath the right normal-appearing buccal mucosa. T2-weighted magnetic resonance imaging revealed a well-defined, internally homogeneous high-signal area with a maximum diameter of 18 mm. Based on the clinical diagnosis of mucocele, the buccal lesion was excised. Histopathological, immunohistochemical and fluorescence *in situ* hybridization analyses revealed the cystic lesion to be a macrocystic SC of a minor salivary gland. SC may have a mucocele-like appearance on magnetic resonance imaging. Even if a non-neoplastic lesion is suspected, the possibility of a malignant lesion such as SC must be considered for salivary gland disease.

Introduction

In 2010, salivary gland carcinoma, a histological type of salivary gland carcinoma with a morphology similar to secretory carcinoma of the mammary gland, was reported as mammary analogue secretory carcinoma (MASC) (1). In 2017, the WHO Classification of Head and Neck Tumors (4th edition) classified MASC as a secretory carcinoma (SC), establishing it as a new histologic type of salivary gland cancer (2). The histological types of salivary gland carcinoma are diverse and often difficult to diagnose. Before the disease classification was established as SC, it was most likely classified as acinic cell carcinoma or cystadenocarcinoma (3). In addition, for the diagnosis of SC, it is crucial to identify the ETV6-NTRK3 fusion gene (EN gene) by molecular biological search in addition to immunohistochemical stains such as S100 and mammaglobin (1).

SC accounts for only 5% of all salivary gland malignancies, and the parotid gland is the predilection site. It is most common in people in their 40s, with a male-to-female ratio of 1.4:1 (4). SC presents as a painless, slow-growing mass (2), and the main treatment is surgical resection. SC is considered a low-grade malignant tumor because the prognosis of SC is generally good, with a 10-year survival rate of 95% and a disease-free survival rate of 89%, although isolated cases of cervical lymph node metastasis and distant metastasis have been reported (4).

To the best of our knowledge, there have been no previous reports of SCs with complete cystic lesions originating from minor salivary glands of the buccal mucosa. Herein, we report a case of SC of minor salivary gland origin in the buccal mucosa, which was suspected to be a mucocele on preoperative imaging examination.

Case report

A 46-year-old man visited the Department of Oral and Maxillofacial Surgery at Saiseikai Senri Hospital in October 2022 with a chief complaint of swelling of the right buccal mucosa. He had been aware of the swelling for approximately 18 months. However, he left it untreated because it was painless. As the swelling gradually increased in size, he opted to visit the Department of Oral and Maxillofacial Surgery at Saiseikai Senri Hospital. The patient's current medical history included hypertension and cerebral infarction, and his only medication was an antihypertensive drug. He was 169.5 cm

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Abbreviations: CK7, cytokeratin 7; FISH, fluorescence *in situ* hybridization; FNAC, fine needle aspiration cytology; MASC, mammary analogue secretory carcinoma; PAS, periodic acid Schiff; SC, secretory carcinoma

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tall and weighed 86.7 kg, with a Body Mass Index of 30.2. On physical examination, there was no obvious facial swelling or perceptual abnormalities (Fig. 1A). Intraoral examinations revealed a submucosal lesion of approximately 20 mm in diameter located anteriorly inferior to the parotid papilla in the right buccal mucosa (Fig. 1B). The lesion was dark blue, elastic hard, painless, submucosally mobile, and did not fade under pressure. Magnetic Resonance (MR) T2-weighted imaging showed a high-signal area with a clear boundary and uniform interior, approximately 18 mm in diameter, within the right buccal mucosa (Fig. 2). Based on our findings, the clinical diagnosis of a mucocele of minor salivary gland origin in the right buccal mucosa was made. However, given the size of the lesion and the length of time since the onset of subjective symptoms, we considered the possibility that it was a malignancy tumor. Therefore, although we did not perform fine needle aspiration cytology (FNAC) before surgery, the lesion, including a portion of the surrounding tissue, was resected under general anesthesia in the month after his initial consultation (Fig. 3).

The resected lesion was grossly cyst-like, with yellowish-brown serous fluid. Hematoxylin-and-eosin (H&E) staining revealed a cystic lesion covered with epithelium (Fig. 4A). The surface of the cystic lesion was predominantly lined with a single cuboidal or cylindrical epithelium layer (Fig. 4B). In some areas, clusters of cells with a pale, foamy cytoplasm invading the fibrous wall were observed (Fig. 4C). Additionally, in some areas, hobnail or papillary growth was evident (Fig. 4D). The cytoplasm was pale, foamy, and vacuolated. Nuclear atypia was not prominent (Fig. 4E). Periodic acid Schiff (PAS) staining revealed that the epithelial cells were negative for both cytoplasmic mucin and cytoplasmic zymogen granules, which are morphological characteristics of mucoepidermoid carcinomas and acinic cell carcinomas, respectively (Fig. 4F). Immunohistochemical analysis using cytokeratin 7 (CK7) and macrophage marker CD163 was performed to rule out the invasive nature of the lesion; clusters of cells invading the fibrous wall were CK7-negative (Fig. 4G) and CD163-positive indicating that the foamy cells were mucophages (Fig. 4H). These histological analyses suggested that the cystic lesion was non-invasive, and differential diagnosis included both benign neoplastic lesions and malignant lesions, such as cystadenoma, intraductal carcinoma, and SC. Immunohistochemical staining showed that the epithelial cells were positive for CK7 (Fig. 4I), S100 (Fig. 4J), and mammaglobin (Fig. 4K), and negative for p63 and DOG1 (not shown). Thereafter, we indirectly confirmed the presence of the *ETV6-NTRK3* fusion using *NTRK3* break-apart fluorescence *in situ* hybridization (FISH) (Fig. 5A), *ETV6* break-apart FISH (Fig. 5B), and pan-TRK immunohistochemistry (Fig. 4L). Thus, the patient was diagnosed with SC. The surgical margins were negative.

Contrast-enhanced CT and FDG-PET/CT performed after the diagnosis of SC showed no cervical lymph node metastasis or distant metastasis (Fig. S1). Ultimately, the patient was diagnosed with stage I secretory cancer (pT1N0M0). Because more than 1 month had passed before the diagnosis was confirmed, the margins of the resected lesion were negative, and the wound was completely epithelialized, no additional resection was performed. One year and 4 months postoperatively, no local recurrence, cervical lymph node metastasis, distant metastasis has been observed.

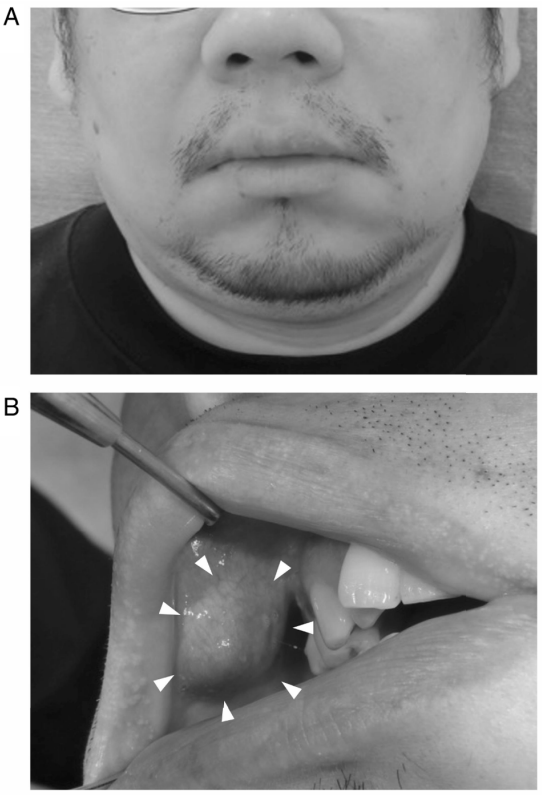

Figure 1. Images from the initial visit. (A) Image of face at the initial visit. No obvious facial swelling was observed. (B) Intraoral image at the initial visit. A submucosal lesion ~20 mm in diameter was found anteriorly inferior to the parotid papilla in the right buccal mucosa (arrowheads).

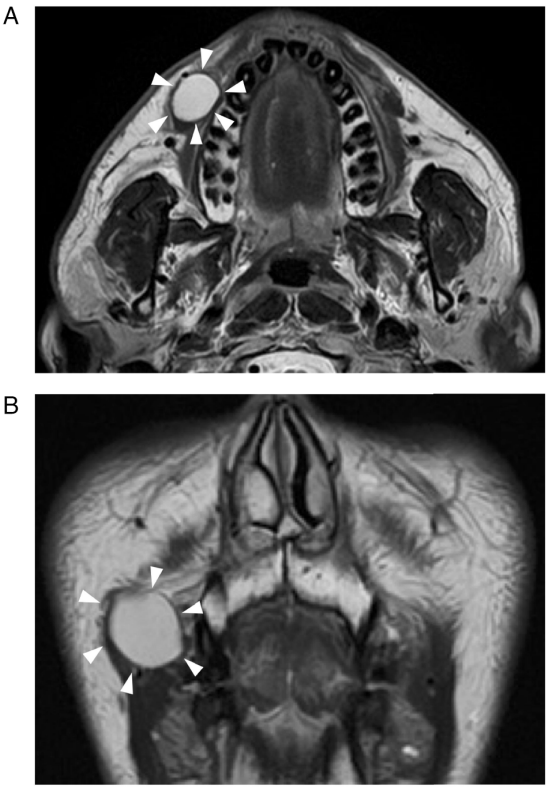

Figure 2. Results of MR imaging. MR T2-weighted imaging showed a high-signal area with a clear boundary and uniform interior, ~18 mm in diameter, within the right buccal mucosa (arrowheads). (A) Horizontal image. (B) Coronal image. MR, magnetic resonance.

Table I. SC with cystic lesion suspected on preoperative imaging.

First author/s, year	Case	Sex	Age, years	Location	MR image	Size	Image diagnosis	Biopsy	FNAC	Treatment	Recurrence	(Refs.)
Gupta *et al*, 2019	1	Male	65	Left parotid	Unilocular	6.2 cm diameter	Cyst	No	No	Resection	No	(15)
Helmy *et al*, 2020	2	Female	11	Right parotid	Unilocular	2.2x2.2 cm	Cyst	No	SC	Resection	No	(16)
Black *et al*, 2020	3	Male	18	Right parotid	Unilocular	2.5 cm diameter	Cyst	No	Benign tumor or cyst	Resection	No	(17)
Shibata *et al*, 2020	4	Female	59	Left Stensen's duct	Unilocular	2.1x2.0x2.3 cm	Stensen's duct cyst	No	No	Resection	No	(18)
Present study	5	Male	46	Right buccal mucosa	Unilocular	1.8 cm diameter	Mucocele	No	No	Resection	No	-

FNAC, fine-needle aspiration cytology; MR, magnetic resonance; SC, secretory carcinoma.

Figure 3. Resected lesion. Scale bar, 5 mm.

Discussion

Cystic salivary gland diseases that occur in the buccal submucosa and other minor salivary gland areas include mucoceles; ductal, epidermoid, dermoid, and lymphoepithelial cysts; cystadenoma; cystic polymorphous adenoma; and intraductal, low-grade mucoepidermoid, and acinic cell carcinomas (5-8). In this case, because MRI T2-weighted imaging performed in the preoperative examination showed a high-signal image with clear boundaries and a homogeneous interior, and the lesion was painless and mobile, a non-neoplastic mucocele was suspected and excision was performed. Subsequently, H&E staining ruled out non-neoplastic lesions, and immunostaining results led to strongly suspected SC. Break-apart FISH analysis confirmed the presence of the EN gene. Furthermore, the cystic epithelium was positive for pan-TRK staining, which supported the presence of the NTRK gene, and this case was diagnosed as SC (Figs. 4 and 5) (9-12). Differentiating SC from acinic cell carcinoma is sometimes difficult, and it is important to confirm the presence of Zymogen granules by immunostaining for DOG1 and PAS staining if needed (13).

SC may present with a mucocele-like appearance on MRI, and FNAC is considered when salivary gland cystic disease is suspected. One of the limitations of this study is that we did not perform FNAC, which would have been useful for preoperative diagnosis (14). In total, four cases of SC with suspected cystic disease on preoperative imaging examination have been reported in the past (Table I) (15-18). Of the two patients who underwent preoperative FNAC, the EN gene was detected in one case, and the diagnosis of SC was made. In contrast, the other patient was not diagnosed with malignant lesions. The other two patients who did not undergo FNAC had preoperatively suspected cystic lesions or benign tumors. Therefore, performing FNAC does not guarantee preoperatively diagnosis of SC. The preoperative diagnosis of salivary gland malignancies is very difficult to make because of the infrequency of salivary gland malignancies themselves, the rarity of SC, and the frequent absence of pain symptoms that characterize many malignancies. For this reason, the possibility of malignancy must always be considered when salivary gland disease is suspected. FNAC for salivary gland disease has a sensitivity of 89-100% and specificity of

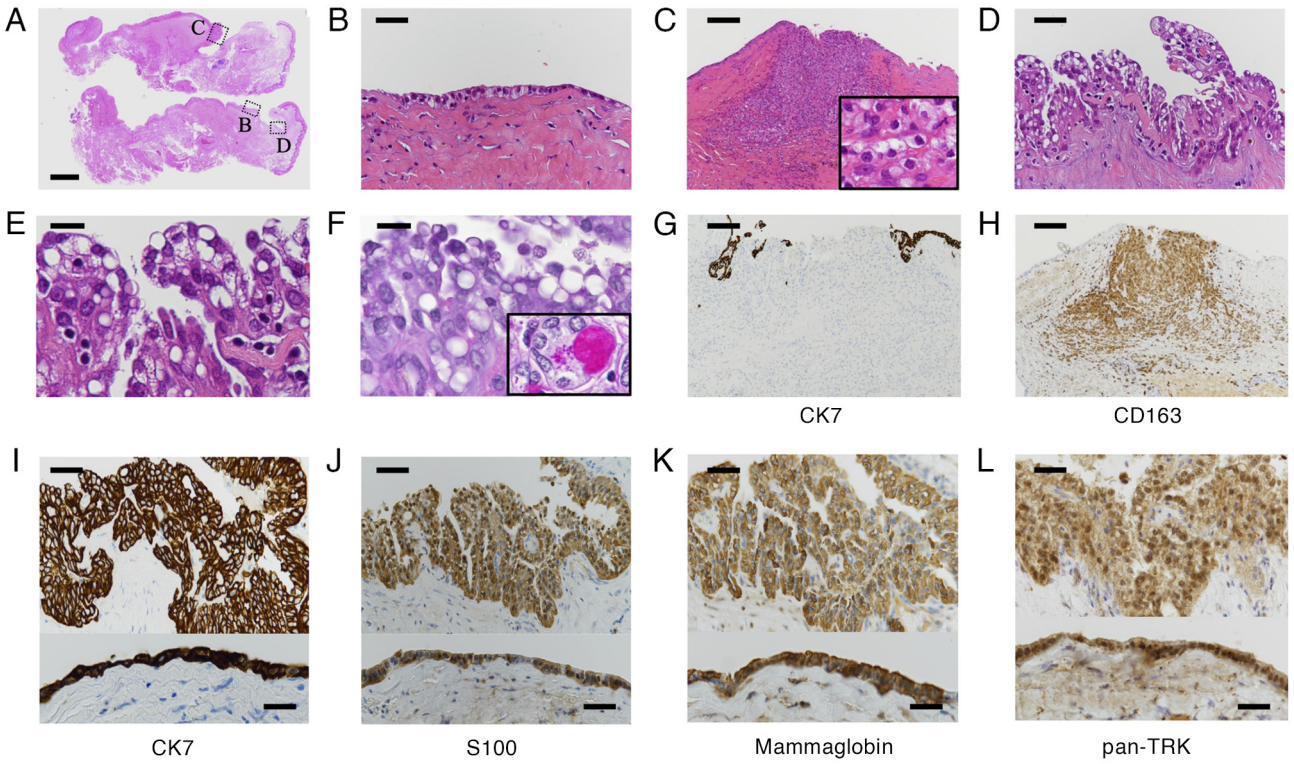

Figure 4. Microscopic findings of the surgically resected tumor. (A) Loupe image of the resected tissue. The lesion was covered with cuboidal or cylindrical epithelium with focal hobnail or papillary growth. Each of the dashed line squares (B-D) are also shown at higher magnification. (B) Component of the cystic lesion covered with flat cuboidal or cylindrical epithelium. (C) Clusters of cells invading the fibrous wall. Inset, higher magnification (x400) of the cells. The invading cells had pale and foamy cytoplasm. (D) Component of the cystic lesion covered with epithelium showing hobnail and papillary growth. (E) Higher magnification of (D). The cytoplasm of the epithelium was pale, foamy and vacuolated. Nuclear atypia was not prominent. (F) PAS staining. Epithelial cells were negative for both cytoplasmic mucin and zymogen granules. Inset: Positive control (magnification, x400), cytoplasmic mucin and zymogen granules in a normal acinar cell. (G and H) Immunohistochemistry of clusters of cells invading the fibrous wall using anti-CK7 and CD163 [same area as in (C)]. Invading cells were (G) negative for CK7 and (H) positive for CD163. (I-L) Immunohistochemistry against (I) anti-CK7, (J) anti-S100, (K) anti-mammaglobin and (L) anti-pan-TRK. The upper panel shows an area with papillary growth in (D), and the lower panel shows an area with flat epithelium in (B). (A-E) H&E staining images. Scale bar, 2 mm (A), 25 μm (B, D and I-L), 50 μm (C, G and H) or 10 μm (E and F). CK7, cytokeratin 7; TRK, tyrosine receptor kinase; PAS, periodic acid Schiff.

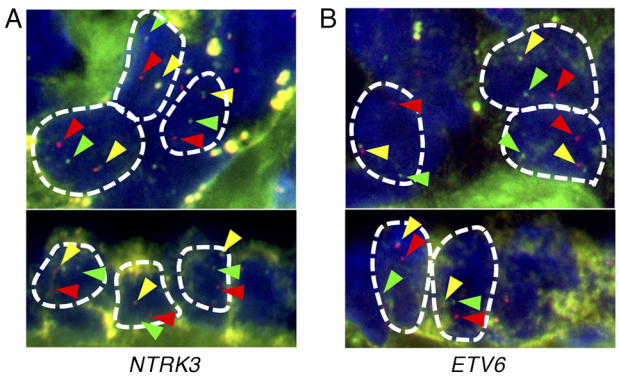

Figure 5. Fluorescence *in situ* hybridization with (A) *NTRK3* break-apart probe and (B) *ETV6* break-apart probe. The break-apart probe shows one separate red (red arrowhead) and green (green arrowhead) signal per cell (dashed lined), which was considered positive for rearrangement. The fused red-green (yellow arrowhead) signal was considered normal (magnification, x600). Upper panel, area with papillary growth. Lower panel, area with flat epithelium.

85-92% (19), and some reports indicate that FNAC for salivary gland cystic disease in particular is more accurate than for all salivary gland lesions (14).

While there have been reports of the macrocystic form of SC in major salivary glands, there have been no reports thereof in minor salivary glands of the buccal mucosa, as in the present case. The reports of macrocystic SC in major salivary glands showed that tumor cells lining the lumen of the cyst may be reduced or not infiltrate the surrounding area, thus making it difficult to distinguish them from mucoceles or ductal cysts on histopathologic H&E staining; immunohistochemical findings targeting S-100 and mammaglobin and molecular biological searches targeting the EN gene are therefore important for diagnosis (13). Our case demonstrated the presence of the macrocystic form of SC in minor salivary glands. Both major and minor salivary glands may show mucocele-like images on MR imaging and it is therefore important to always include clinical and histopathological investigations for malignancy in cystic lesions in the minor salivary glands, without excluding the possibility of neoplastic lesions. The patient currently has no signs of recurrence and metastasis, and the prognosis is considered good. However, further studies are needed to accumulate more cases.

In conclusion, in this report, we described a case of SC, of minor salivary gland origin, in the buccal mucosa and reviewed related literature. The unique characteristics and treatment considerations highlighted in this case contribute valuable insights to the field of oral oncology.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

The manuscript was produced and reviewed by all authors collectively. TC and YM confirm the authenticity of all the raw data. TC, ATN, YU, TK, KW, SK, YM and NU designed the study. TC, ATN, YU, KW, SK, YM and NU wrote the manuscript. TC, KW and TK were involved in patient care. YU and KH were the pathologists in charge of the case. All authors agreed to be held accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient has been informed that there is no risk to their anonymity in association with the publication of this report. Written informed consent was obtained from the patient for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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