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Case Report

Secretory carcinoma around Stensen's duct misdiagnosed as salivary duct cyst

Eri Shibata[1], Kei-ichi Morita[1,4], Kou Kayamori[2], Mayuko Maruiwa[1], Yasuyuki Michi[3], Yukiko Sato[5], Kengo Takeuchi[5,6], Tohru Ikeda[2], Hiroyuki Harada[3], Tetsuya Yoda[1]

Departments of [1]Maxillofacial Surgery, [2]Oral Pathology, [3]Oral and Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; [4]Bioresource Research Center, Tokyo Medical and Dental University, Tokyo, Japan; [5]Department of Pathology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Division of Pathology, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan

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Abstract: Secretory carcinoma (SC) of the salivary gland was identified in 2010, and it is characterized by a specific *ETV6* gene arrangement. The most common primary site for SC is the parotid gland; however, SC around the Stensen's duct is rare. Here we describe a rare case of a SC around the Stensen's duct that was initially misdiagnosed as a salivary duct cyst. A 59-year-old woman presented with a mass in the region of the left parotid papilla. Magnetic resonance imaging (MRI) revealed a well-circumscribed lesion and enhancement with a rim and an inner wall-like part that appeared in the late phase. Based on the initial clinical and imaging findings, a salivary duct cyst of the parotid gland was diagnosed. However, the lesion was histopathologically diagnosed as a SC based on immunohistochemical findings. The tumor cells showed diffuse positive staining for AE1/AE3, vimentin, and mammaglobin and focal positive staining for S-100 protein, SOX-10, and DOG-1. Fluorescence *in-situ* hybridization revealed *ETV6* gene rearrangement in the tumor. In cases of cystic lesions around the Stensen's duct, clinicians should bear in mind that the possibility that they could be minor salivary gland cancers, such as SC.

Keywords: Secretory carcinoma, *ETV6* gene arrangement, Stensen's duct, salivary duct cyst, mammaglobin

Introduction

A mammary analog secretory carcinoma (MASC) is a recently defined salivary gland tumor reported by Skalova *et al.* [1]. It is so named because its histological features resemble those of a secretory carcinoma (SC) of the breast because it shares the *ETV6-NTRK3* translocation, (12;15) (p13;q25). The new 2017 World Health Organization Classification of head and neck tumors defines MASC as SC to standardize the nomenclature across organ sites [2]. The leading primary site for SCs is the parotid gland, followed by the oral cavity, submandibular gland, and accessory parotid gland. In the oral cavity, the lip, soft palate, and buccal mucosa are the most commonly affected subsites [1]. To date, several retrospective studies and case reports of SC have been published; however, there has been no report of SCs around the Stensen's duct. Here, we report a rare case of an SC around the Stensen's duct that was initially misdiagnosed as a salivary duct cyst.

Case report

A 59-year-old woman was referred to our department with a 5-month history of painless swelling on the left side of the buccal mucosa. Her past medical history included a hysterectomy with bilateral salpingo-oophorectomy followed by six courses of chemotherapy, consisting of doxorubicin and cisplatin, for endometrial cancer 10 years before. She had no history of smoking or drinking. At her first visit, we detected a mass measuring 30 mm in the region of the left parotid papilla, but the mucosal surface was normal. The parotid duct opening was not appreciated, and no saliva was expressed

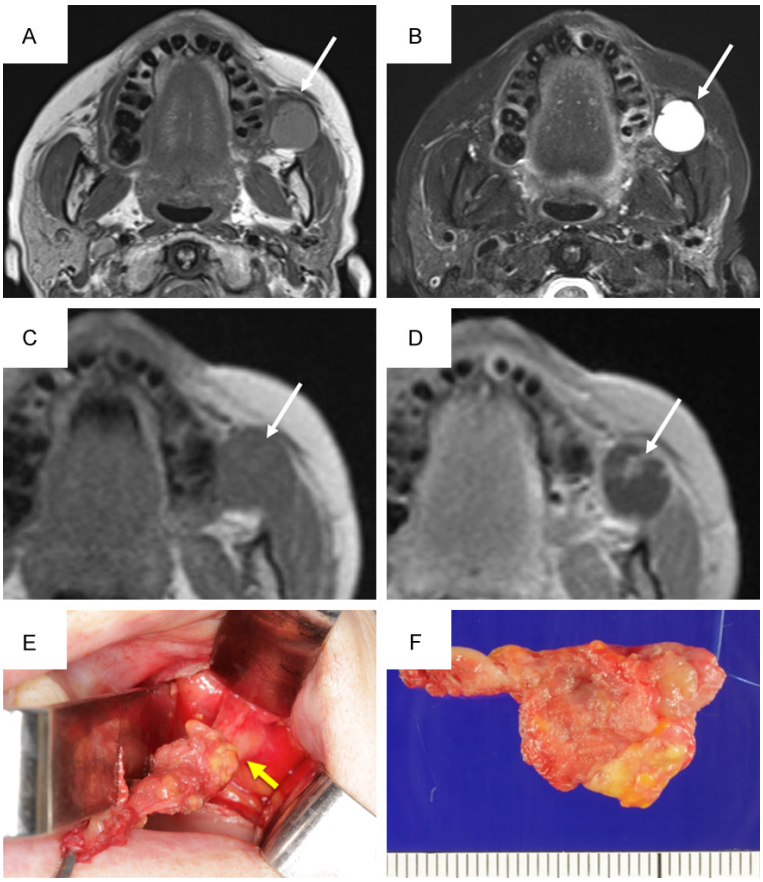

Figure 1. Image and surgical findings. (A) The T1-weighted imaging revealed a lesion with a slightly higher intensity (arrow) than that of the muscle. (B) The T2-weighted, fat-suppressed imaging revealed a high intensity lesion (arrow). (C and D) Dynamic Gd-enhanced MRI revealed enhancement with a rim and an inner wall-like part (arrow) during the late phase (D) but not the early phase (C), and most of the lesion's inner part was not enhanced. (E) Surgical findings. The mass with a part of buccal mucosa including the parotid papilla was removed and ligated at the normal parotid duct (arrow). (F) Gross view of the resected specimen.

upon manipulation. Magnetic resonance imaging (MRI) revealed a well-circumscribed lesion that was 21 mm × 20 mm × 23 mm in size. The posterior aspect of the lesion contacted the anterior edge of the masseter muscle, and the distal aspect of the lesion contacted the buccinator muscle. The T1-weighted imaging revealed a lesion with a slightly higher intensity than that of the muscle, and T2-weighted, fat-suppressed imaging revealed a high-intensity lesion (**Figure 1A** and **1B**). Dynamic Gd-enhanced MRI revealed enhancement with a rim and an inner wall-like part that appeared during the late phase but not the early phase, and most of the lesion's inner part was not enhanced (**Figure 1C** and **1D**). Compared with the right parotid gland, the left side displayed atrophy (**Figure 1A** and **1B**). In addition, sialography revealed obstruction of the Stensen's duct (data not shown). Based on clinical and imaging findings, we initially diagnosed the patient with a salivary duct cyst of the parotid gland. Accordingly, cystectomy was performed with the patient under general anesthesia. The lesion was removed, along with a part of the buccal mucosa, including the parotid papilla. The mass adhered to the surrounding tissues, and a capsule was not observed (**Figure 1E**). Gross examination of the surgical specimen revealed involvement of Stensen's duct by the mass (**Figure 1F**).

Upon microscopic evaluation, the cystic structures of the tumor tissues, which were partially lined with tumor nests, and the cystic wall involved a large excretory duct, the Stensen's duct, and minor salivary glands (**Figure 2A**). Macrocystic cavities were focally lined with tumor nests that exhibited microcystic or papillary structures. No epithelium other than tumor nests lined the macrocystic cavities. We detected a few periodic acid-Schiff positive zymogen granules digested by diastase in the tumor cells (data not shown).

In addition, the tumor displayed diffuse positive staining for AE1/AE3 (**Figure 2A**), vimentin (**Figure 2C**), and mammaglobin (**Figure 2D**). Staining for S-100 protein (**Figure 2E**), SOX-10 (**Figure 2F**), and DOG-1 (**Figure 2G**) was focally positive, whereas staining for α-SMA, p63, and p40 was negative. The Ki-67 index was 7% (82/1166). Fluorescence *in-situ* hybridization revealed *ETV6* gene rearrangement (**Figure 2H**). Furthermore, *ETV6-NTRK3* fusion transcripts were detected by reverse transcription-polymerase chain reaction (RT-PCR) and se-

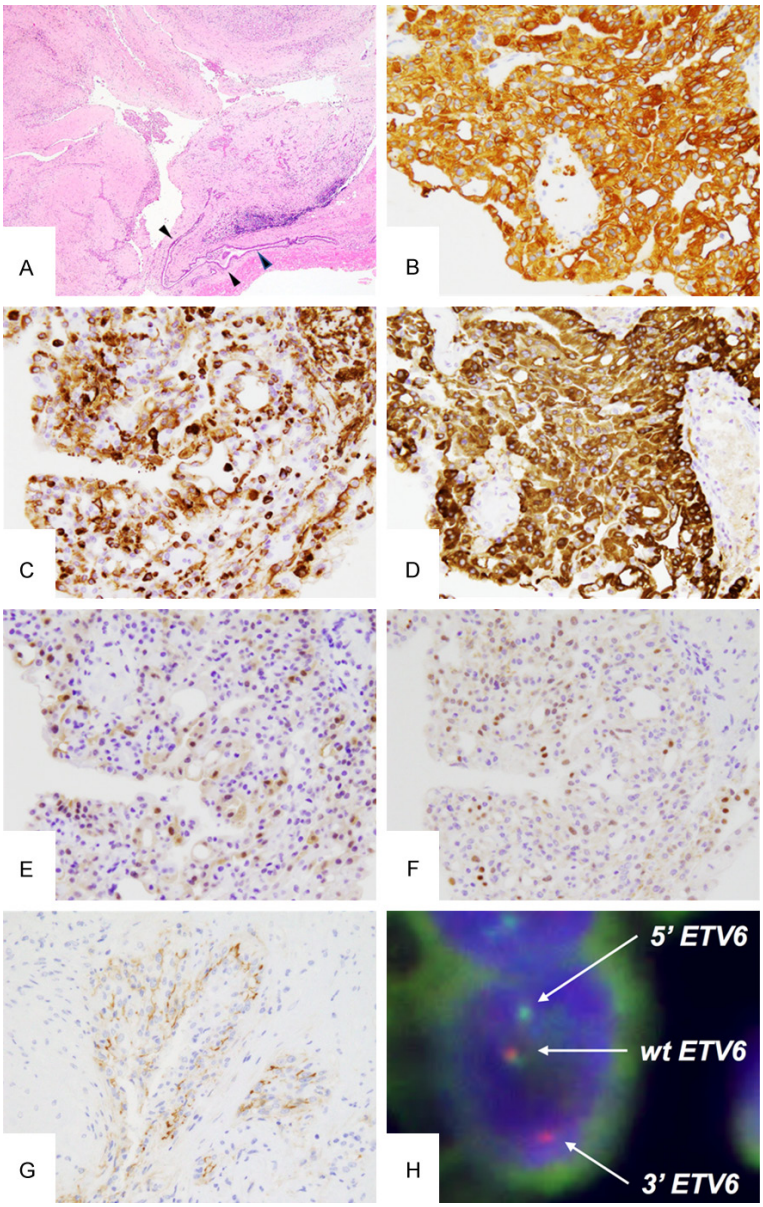

Figure 2. Histologic findings. (A) H&E staining. An anatomical arrangement of tumor tissues. The cystic structures of the tumor tissues, which were partially lined with tumor nests, and the cystic wall involved a large excretory duct (arrowheads). (B-G) Immunohistochemical studies showed that tumor tissues displayed diffuse positive staining for AE1/AE3 (B), vimentin (C) and mammaglobin (D). Staining for S-100 (E), SOX-10 (F), and DOG-1 (G) was focally positive. (H) *ETV6* split. For Fluorescence *in situ* hybridization (FISH), unstained sections (4 μm thick) were subjected to hybridization with the bacterial artificial chromosome (BAC) clone-derived probes for *ETV6*, which were differentially labeled with FITC (green) (RP11-639O1, RP11-1077I5) and Texas Red (red) (RP11-297N18). The hybridized slides were then stained with DAPI and examined using a BZ-Z710 fluorescence microscope (Keyence, Osaka, Japan).

quencing of PCR products (**Figure 3A** and **3B**). Hence, the tumor was reclassified as SC. Subsequently, additional resection was performed, but tumor cells were not found in the additionally resected specimens. Moreover, no evidence of recurrence or metastasis was noted 3 years postoperatively.

Discussion

SC is a recently defined salivary gland carcinoma that is characterized by an *ETV6-NTRK3* translocation [3]. The *ETV6-NTRK3* fusion gene encodes a chimeric oncoprotein tyrosine kinase that activates the phosphatidylinositol 3-kinase-Akt pathway and the mitogen-activated protein kinase pathway [4]. Formerly, because of their nearly identical histological growth patterns, SCs were frequently classified as acinic cell carcinomas (AcCC). According to previous reports, SCs comprise microcystic, papillary cystic, or solid structures and zymogen-poor types [5]. At present, the papillary cystic structure is considered rare in true AcCC but common in SC. Differentiating SC from AcCC based only on morphologic features is challenging. However, their immunohistochemical profiles display some differences. Compared with AcCCs, SCs tend to exhibit strong expression of mammaglobin, vimentin, and S-100 protein, and they are normally negative for DOG1 and p63; however, AcCCs display opposite staining features [1, 2, 6-8]. Nevertheless, no marker is specific for SC. Our immunohistochemical study demonstrated that SC cells showed focal positivity for S-100 protein and DOG1. As described above, generally, SCs are generally immunohistochemically strongly positive for S-100 protein and negative for DOG1. However, the degree of pos-

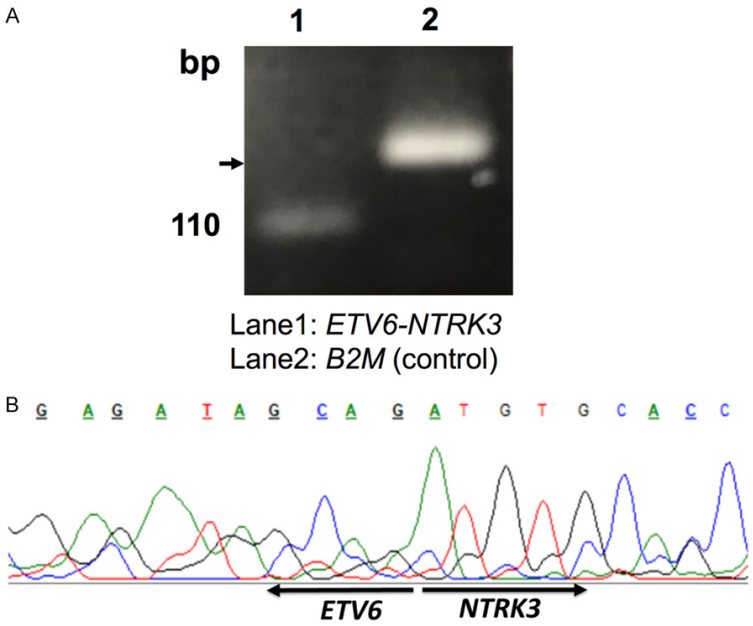

Figure 3. A. Reverse transcription-polymerase chain reaction analysis of *ETV6-NTRK3*. The tumor showed the *ETV6-NTRK3* fusion transcript of 110 bp (Lane 1). B. Sequencing results. Arrowhead, the fusion point of the *ETV6-NTRK3*.

itivity for these antibodies varies from case to case. Connor *et al.* [9]. demonstrated that two out of seven SC cases exhibited weak focal staining for S-100 protein. Moreover, Stevens *et al.* reported that 10 out of 12 SC cases showed weak DOG1 expression limited to the periphery of the tumor nests [10]. Our case is consistent with these previous studies.

Although SC occurs in the parotid gland in most cases, cases of SC in other locations have also been reported [1, 11]. A recent study suggested that most non-parotid AcCCs could be SCs [12]. In 1927, Goforth first reported squamous cell carcinoma (SCC) arising from Stensen's duct; to date, only 33 cases of neoplasm of the Stensen's duct have been reported (**Table 1**) [13-17]. Of 31 acknowledged cases (including our case), various histologic types exist, including SCC, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, carcinosarcoma, and undifferentiated carcinoma. All reported cases were malignant tumors. In addition, the reported sizes of Stensen's duct tumors ranged from 5 to 45 mm. Almost all cases were treated surgically. Although it is often difficult to determine the origin of a buccal tumor, Carpenter *et al.* [18] stated that "only those tumors causing a localized swelling along the path of the duct or obstructing the duct and producing symptoms of parotitis, can be considered as primary tumors of the Stensen's duct" [18]. In our case, imaging findings and the gross examination revealed the tumor arising in the distal segment of the Stensen's duct. Furthermore, compared with the right parotid gland, the left side displayed atrophy on MRI, and sialography confirmed obstruction of the Stensen's duct. Based on a symptom of the disturbance of secretion of saliva from the Stensen's duct and radiological obstruction of the Stensen's duct, we speculated that this SC originated from the Stensen's duct. On the other hand, a cystic lesion lined with tumor cells was found near the Stensen's duct, but a direct histologic connection of the cystic lesion with the Stensen's duct was not evident. Therefore, there is a possibility that this case originated from a minor salivary gland near the parotid papilla and invaded into the Stensen's duct.

As reported, the prognosis for SCs is poorer than that for AcCCs, and the local recurrence, lymph node metastasis, and distant metastasis rates are 15%, 20%, and 5%, respectively [1]. Thus, it is imperative to differentiate between SCs and AcCCs. In the future, we might use a new targeted therapy, such as entrectinib, which inhibits TrkA, TrkB, TrkC, ROS1, and ALK tyrosine kinase [19-21]. Initially, we considered the translocation of the *ETV6-NTRK3* gene rearrangement to be a discrete feature of SC. It is worth mentioning that in 2018, Skalova *et al.* reported 10 cases that were morphologically and immunohistochemically typical of SC, harboring an *ETV6-RET* fusion [22]. Subsequently, Guilmette *et al.* recently described a dual *ETV6-NTRK3* and *ETV6-MAML3* translocation in an SC case and an *ETV6-RET* fusion in three SC cases [23]. Additionally, Rooper *et al.* [24] reported an *ETV6-MET* translocation. In most cases, distinguishing SC from AcCC using only hematoxylin and eosin staining is challenging.

Table 1. Stensen's duct neoplasm cases

Author	Age	Sex	Diagnosis	Long diameter (mm)	Treatment
Goforth	60	F	SCC	10	Local excision + RT
Figi and Rowland	62	M	AC	5	Local excision + RT
Lyall and Golomb	40	M	SCC	35	RT
Smith et al.	29	M	Sarcoma	15	Local excision
Beyer et al.	40	F	AC	15	Local excision + RT
Beyer et al.	58	F	AC	20	Local excision
Peracchio	51	F	SCC	15	RT
Maisel et al.	53	M	SCC	5	Local excision, ND
Gaisford et al.	55	F	MEC	NS	Parotidectomy, ND
Gaisford et al.	25	F	MEC	NS	Parotidectomy + RT
Gaisford et al.	NS	M	MEC	NS	Parotidectomy
Wolfe	60	M	SDC	30	Parotidectomy
Clairmont et al.	53	F	MEC	10	Parotidectomy
Clairmont et al.	48	F	ACC	45	Parotidectomy
Polayes and Rankow	42	M	MEC	NS	Parotidectomy
Polayes and Rankow	51	M	MEC	NS	Parotidectomy
Vigorita et al.	82	M	SCC	22	Parotidectomy, ND
Owens et al.	62	M	SCC	15	Parotidectomy + RT
Frechette et al.	24	M	UC	NS	Parotidectomy + RT
Carpenter et al.	49	M	ACC	10	Parotidectomy + RT
Lari et al.	58	M	AC	NS	Unknown
Haar et al.	57	M	MEC	10	Parotidectomy
Kapadia et al.	15	F	RMS	15	Parotidectomy + chemotherapy
Steiner et al.	70	M	SCC	15	Local excision
Munoz-Guerra et al.	38	M	UC	30	Parotidectomy, ND + RT
Giger et al.	61	F	MEC	15	Parotidectomy
Tomimnaga et al.	67	M	SCC	NS	Resection
Wakoh et al.	62	M	SCC	NS	Resection
Kim et al.	47	M	SCC	NS	Parotidectomy + RT
Okada et al.	56	M	SDC	NS	Resection
Matsushita et al.	71	M	SCC	33	Local excision, ND
Eranga et al.	76	F	SDC	NS	Local excision
Mohamed et al.	74	M	PC	20	Parotidectomy
Our case	59	F	SC	20	Local excision

AC, adenocarcinoma; ACC, adenoid cystic carcinoma; MEC, mucoepidermoid carcinoma; RMS, rhabdomyosarcoma; SCC, squamous cell carcinoma; SDC, salivary duct carcinoma; UC, undifferentiated carcinoma; PC, papillary carcinoma; SC, secretory carcinoma; NS, not stated; RT, radiation therapy; ND, neck dissection.

In cases of cystic lesions around the Stensen's duct, clinicians should bear in mind the possibility of a minor salivary gland cancer, such as SC. Imaging plays a limited role in identifying a cystic malignant lesion with few cellular components, so comprehensive examinations, including genetic examination and immunohistochemical staining, must be carefully performed.

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Disclosure of conflict of interest

None.

Address correspondence to: Kei-ichi Morita, Department of Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Tel: +81-3-5803-5498; Fax: +81-3-5803-0298; E-mail: keiichi.m.osur@tmd.ac.jp

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