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Clinicopathologic characterization of secretory carcinoma of salivary gland

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Abstract

Background To investigate the clinicopathologic characteristics, therapeutic methods, and prognosis of secretory carcinoma of salivary gland (SCSG).

Methods The clinicopathologic data of 13 patients with SCSG admitted to Shanxi Cancer Hospital from January 2018 to June 2023 were retrospectively analyzed, and a literature review was performed.

Results A total of eight males and five females aged 22–78 years old were enrolled, and they commonly presented with painless masses in the parotid or submandibular gland. They all underwent surgical treatment, accompanied by typical pathological examinations postoperatively. Fluorescence in situ hybridization (FISH) was conducted in seven cases, the results were all positive, and no gene fusion other than ETV6-NTRK3 was found. Two patients developed local relapse during follow-up, both of which were in the surgical area. By the end of the follow-up, 12 patients survived and one patient died.

Conclusions SCSG is a rare low-grade malignancy with a good prognosis. Pathological and immunohistochemical characteristics are the key to secretory carcinoma (SC) diagnosis, and surgical excision is the major treatment means for SCSG. Whether to perform simultaneous cervical lymph node dissection and other adjuvant therapies should be determined based on the pathological stage and the presence or absence of high-risk factors.

Keywords Secretory carcinoma, Salivary gland tumor, Mammary analog secretory carcinoma

Introduction

Secretory carcinoma of salivary gland (SCSG) is a rare malignancy that has recently been recognized. First proposed by Skalova et al. [1] in 2010, SCSG was noted to share histomorphological and immunohistochemical (IHC) characteristics with mammary secretory carcinoma (SC), leading to its initial designation as mammary analog secretory carcinoma (MASC). In the fourth edition of the World Health Organization (WHO) Classification of Head and Neck Tumors in 2017, MASC was listed as a new classification in salivary gland tumors, and officially named SC [2]. Most cases of SCSG exhibit morphological similarities to mammary SC and are characterized by the presence of the ETV6-NTRK3 gene fusion, and it was often misdiagnosed as acinic cell carcinoma

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(AciCC), adenoid cystic carcinoma (ACC), and mucoepidermoid carcinoma (MEC) previously [3, 4]. Currently, SCSG is mostly reported by individual cases or small series of reports in China and internationally, and limited research is available on its clinicopathologic characteristics, treatment, and prognosis. In this study, we retrospectively analyzed the clinical data of 13 patients with SCSG, summarizing the clinical features, morphological characteristics, differential diagnosis, treatment approaches, and prognosis. Our aim is to enhance the understanding of SCSG and provide new insights for the standardized diagnosis and treatment of SCSG.

Table 1 Clinicopathologic characteristics of patients ($n=13$)

Basic characteristic	$n=13$
Median age (years,range)	47 (22–78)
Gender (male:female)	8:5
Tumor location (n, %)	
Parotid gland	9 (69.23)
Submandibular gland	3 (23.08)
Palate	1 (7.69)
Clinical manifestation (n, %)	
Painless masses	13 (100%)
Tumor characteristics	
Diameter(cm,range)	2.2 (1.5-5.0)
Texture	Hard
Boundary	Clearer
Activity	Good
T stage(n,%)	
T1	3 (23.08)
T2	6(46.15)
T3	3(23.08)
T4	1(7.69)
N stage(n,%)	
N0	11(84.62)
N1	1(7.69)
N2	1(7.69)
N3	0
M stage(n,%)	
M0	13(100)
M1	0
IHC(n,%)	
Mammaglobin(+)	11 (11/13)
S-100(+)	13 (13/13)
MUC-4(+)	6 (6/10)
CK7(+)	13 (13/13)
AE1/AE3(+)	13 (13/13)
P63(-)	9 (9/12)
Dog-1(-)	12 (12/13)
Ki-67	10 (2–15%)
FISH genetic testing(n,%)	
ETV6-NTRK3 Fusion	7 (7/7)

Materials and methods

Clinical data

Clinical data of 13 patients with head-neck SCSG admitted to Shanxi Cancer Hospital from January 2018 to June 2023 were retrospectively analyzed. These patients were all pathologically diagnosed with SC according to the fourth edition of the WHO Classification of Head and Neck Tumors, and had complete medical records and follow-up data. Exclusion criteria: (1) with other malignancies, (2) clinicopathologic data missing, and (3) died due to surgery-related complications within three months postoperatively. Patients all gave informed consent and signed an informed consent form.

Therapeutic methods

The therapeutic method was determined by multi-disciplinary team (MDT) discussion based on specific tumor stage, site, and basic conditions of patients. For patients who had undergone simple primary tumor resection at other hospitals before being referred to our institution, the treatment plan was determined based on a comprehensive evaluation of prior imaging and pathological examinations, surgical records and so on.

Follow-up

The patients were followed up by outpatient clinic visits every three months in the first year postoperatively, and every six months from the second year onwards. For those who did not visit our outpatient facility for follow-up, telephone follow-up was implemented.

Results

Clinical features

Eight males and five females aged 22–78 years old were enrolled, with a median age of onset of 47 years old. SCSG occurred in the parotid gland in nine cases, submandibular gland in three cases, and palate in one case. All patients presented to the clinic with complaints of painless masses which grew slowly, with an average duration from discovery to diagnosis of 21 (8–49) months. Regional lymph node metastasis occurred in two cases at the time of diagnosis, and none of the patients developed distant metastasis after SC diagnosis. The clinicopathologic characteristics of patients are shown in Table 1.

Imaging characteristics

Ultrasonographically, SCSG often exhibited heterogeneous hypoechoic masses with a more regular morphology and clear boundaries. It mostly appeared as solid nodules and a few as cystic-solid nodules, with punctate blood flow signals within the lesions. Specifically, solid nodules were observed in nine cases and cystic-solid nodules in four cases.

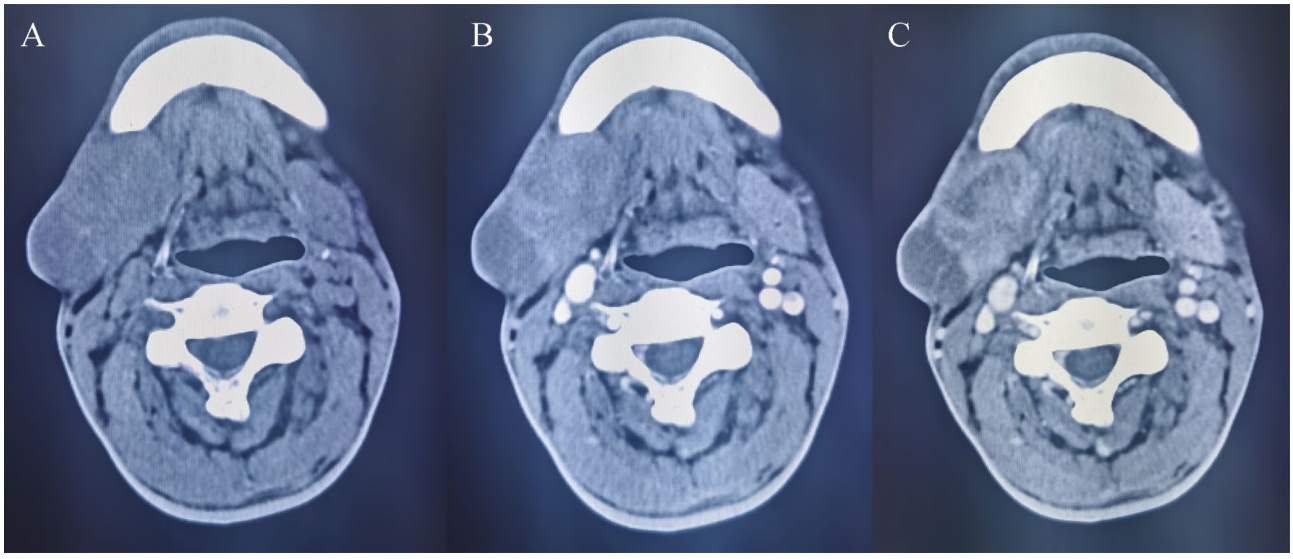

Fig. 1 CT examination of patients with right submandibular SC. **A**: CT plain scan shows irregular mass shadow in the right submandibular gland, with cystic-solid nodules and unclear boundaries; **B** and **C**: Enhancement scan shows uneven enhancement

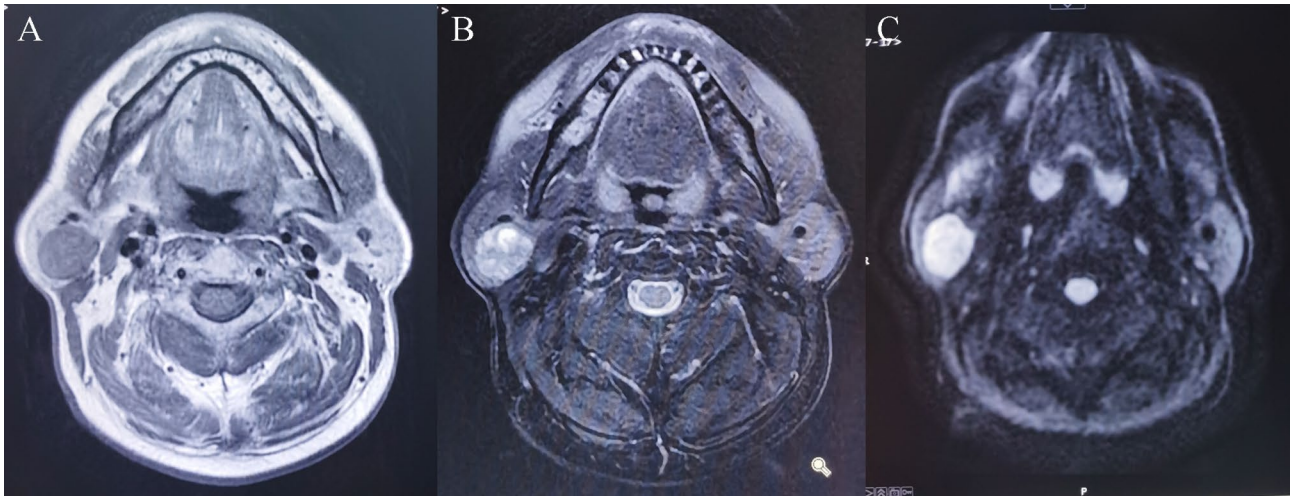

Fig. 2 MRI examination of patients with right parotid SC. **A**: Roundish nodules in the right parotid gland, with clear boundaries, smooth margins, and slightly low signals on T1WI; **B**: Uneven high signals on T2WI; **C**: Obvious high signals on DWI

On Computed Tomography (CT) scan, SCSG usually appeared as oval or lobulated masses with clear boundaries and regular margins. The density was uneven, often with low-density cystic areas, and the lesions showed varying degrees of enhancement on contrast scans. Specifically, six cases showed uneven and obvious enhancement, and three cases showed mild enhancement. Typical CT features are shown in Fig. 1A and C.

On Magnetic Resonance Imaging (MRI) scan, SCSG typically presented as oval or nodular masses with clear boundaries, high signals on fat-saturated images, and low signals on apparent diffusion coefficient (ADC) images. Cystic components of varying degrees were also observed, with high signals on both T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI), while the solid components showed medium to low signals on T2WI. Specifically, three cases displayed long or mixed long and short signals on T1WI or T2WI, with high signals on fat-saturated images, and uneven, mild, or obvious enhancement. Typical MRI features are shown in Fig. 2A and C.

Pathological characteristics

Macroscopically, nine cases had solid lesions with a hard texture, clear boundaries, and off-white or grayish-yellow sections. Four cases presented cystic-solid lesions with light-brown liquid in the cystic areas. As could be seen by hematoxylin-eosin (HE) staining, the cells were arranged in lobulated, microcystic, nodular, vacuolated, and mammillary structures, and obvious luminal secretion could

be seen in some areas, with hyperplastic fibrous tissues in the surroundings. Under high magnification, the tumor cells were uniform in size, round or oval, with eosinophilic granular or vacuolated cytoplasm, clear nuclear membranes, small and uniform nuclei, and occasional vascular cancer emboli, mitoses, and necrosis. No obvious zymogen granules were observed. The results of IHC revealed that 13 cases were diffusely positive for S-100, CK7, and AE1/AE3, 11 cases were strongly positive for mammaglobin, six cases had MUC4(+), nine cases had P63(-), and 12 cases had Dog-1(-), and the positive rate of Ki-67 was 2-15%. Besides, characteristic ETV6-NTRK3 gene fusion was exposed by FISH in seven cases. Representative HE staining and IHC can been seen in Fig. 3A and H. Detailed results of IHC are displayed in Table 2.

Treatment and survival status

Thirteen cases underwent surgical treatment, all of which achieved radical operation(RO) resection. The specific treatments and follow-up outcomes are detailed in Table 3. Among these cases, four patients initially had simple excisions performed at other hospitals and were subsequently referred to our hospital after a pathological diagnosis of SC. Of these, three patients underwent secondary extended resection with cervical lymph node dissection. Postoperative findings showed no residual cancer cells in two cases, while the remaining case revealed residual cancer cells with regional lymph node metastasis. The multidisciplinary team (MDT) recommended regular follow-ups without the need for further surgery for the fourth patient. The remaining nine cases underwent primary lesion excision, with four of them also receiving simultaneous cervical lymph node dissection. One patient, who presented with a left periauricular mass, was treated with a left parotidectomy, excision of the marginal mandibular branch of the facial nerve, and left cervical lymph node dissection. Postoperatively, this patient was pathologically diagnosed with SC. It was later discovered that the patient had undergone a left buccal mass excision and skin grafting from the right lower

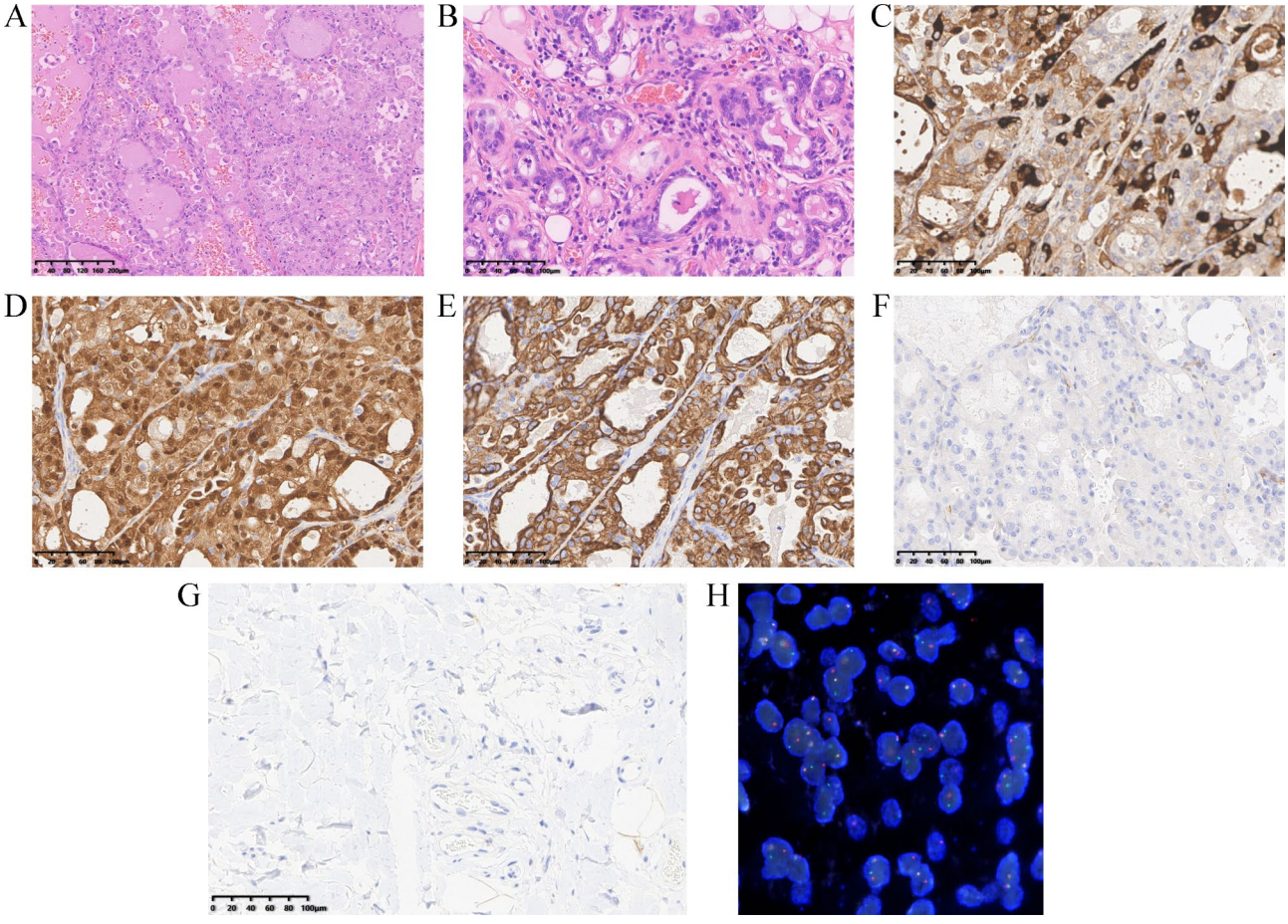

Fig. 3 Pathological examination of parotid SC patient. **A**: Tumor cells arranged in a lobulated and nodular pattern with surrounding fibrous tissue proliferation, HE ×10; **B**: Under high magnification, tumor cells are relatively uniform in size, round or oval in shape, with eosinophilic granular cytoplasm, distinct nuclear membranes, and visible nucleoli, HE×20; **C**: Mammaglobin(+), ×20; **D**: S-100 (+), ×20; **E**: CK7 (+), ×20; **F**: Dog-1 (-), ×20; **G**: Ki-67 approximately 10% ,×20; **H**: ETV6 gene breakage

Table 2 IHC characteristics of 13 SCSG cases

Case	Mammaglobin	S-100	MUC-4	CK7	AE1/AE3	P63(-)	Dog-1	Ki-67	FISH
1	+	+	+	+	+	+	-	10%	Fusion
2	+	+	+	+	+	-	-	8%	NP
3	+	+	NP	+	+	+	-	10%	NP
4	+	+	-	+	+	+	-	5%	Fusion
5	+	+	+	+	+	+	-	2%	NP
6	+	+	-	+	+	-	-	15%	Fusion
7	-	+	-	+	+	+	-	10%	Fusion
8	+	+	+	+	+	-	-	5%	NP
9	+	+	NP	+	+	+	-	10%	NP
10	+	+	NP	+	+	+	-	10%	Fusion
11	-	+	+	+	+	+	-	15%	Fusion
12	+	+	+	+	+	+	+	5%	NP
13	+	+	-	+	+	NP	-	7%	Fusion

Note: NP = Not performed

Table 3 Treatment and follow-up results of 13 SCSG cases

Case	Site	Surgical mode	Lymph node metastasis	Adjuvant therapy	Relapse/metastasis	Follow-up time
1	Left parotid gland	Left parotidectomy and mass excision, excision of marginal mandibular branch of the facial nerve, and left cervical lymph node dissection	Yes	Radiotherapy	No	54 months
2	Left parotid gland	Left superficial parotidectomy and mass excision	-	No	No	39 months
3	Right parotid gland	Right superficial parotidectomy and mass excision, and right cervical lymph node dissection	No	No	Relapse in the surgical area	47 months
4	Right parotid gland	Right parotidectomy and mass excision, and right cervical lymph node dissection	No	No	No	35 months
5	Right parotid gland	Right parotidectomy and mass excision, and right cervical lymph node dissection	No	Radiotherapy	No	28 months
6	Right parotid gland	Right superficial parotidectomy and mass excision	-	No	Relapse in the surgical area with lymph node metastasis	29 months
7	Left parotid gland	Left superficial parotidectomy and mass excision	-	No	No	43 months
8	Right submandibular gland	Right submandibular gland and mass excision, partial mandibulectomy, and right cervical lymph node dissection	Yes	Neoadjuvant chemotherapy, postoperative radiotherapy	No	19 months
9	Right parotid gland	Right superficial parotidectomy and mass excision, and right cervical lymph node dissection	No	No	No	61 months
10	Palate	Extended excision of palatal mass, and biomembrane repair	-	No	No	7 months
11	Right submandibular gland	Right submandibular gland and mass excision, and right cervical lymph node dissection	No	Radiotherapy	No	26 months
12	Right submandibular gland	Right submandibular gland and mass excision	-	No	No	14 months
13	Right parotid gland	Right superficial parotidectomy and mass excision	-	No	No	8 months

abdomen at our hospital before 2009, with a postoperative diagnosis of acinic cell carcinoma (AciCC). Upon reviewing the histopathologic slide of the buccal mass and consulting with pathologists, additional IHC staining was performed, leading to a revised diagnosis of SC.

As of March 2024, all 13 patients were followed up, of which 12 patients survived and one patient died. Two patients had local relapse during follow-up, both of which were in the surgical area and treated with surgery again, and one of which was accompanied by cervical lymph node metastasis. The remaining patients achieved tumor-free survival.

Discussion

SCSG is a low-grade malignancy characterized by features similar to mammary secretory carcinoma (SC) and a distinctive ETV6 translocation [5, 6]. In 2017, SC was officially included in the WHO Classification of Head and Neck Tumors, before which SCSG was mostly misdiagnosed as AciCC, MEC, or other types of salivary gland tumors [7]. Statistics indicate that SCSG is responsible for <0.3% of all salivary gland malignancies, and its incidence may increase with the growing understanding of the disease and advancements in molecular detection techniques [8, 9].

SCSG can occur at any age, but it is more common in adults, with a slight male predominance [10, 11]. SCSG in children is even rarer clinically, and only a few case reports are available in China and beyond [12, 13]. In this paper, the median age of onset was 47 years old, and the male-to-female ratio was 1.6:1, consistent with previous reports. SCSG primarily presents as slow-growing painless masses with a relatively long course, and it may have grown for months or even years before diagnosis. The parotid gland is involved most frequently, responsible for about 75-80% of SCSG, followed by submandibular gland and minor salivary gland, with other sites being less common [14–16]. In our study, SCSG occurred in the parotid gland in nine cases, submandibular gland in three cases, and palate in one case. None of these cases showed nerve involvement, consistent with other findings. A review of the current literature on secretory carcinoma of salivary glands see Table 4 [3, 11, 13–40].

Ultrasound, CT and MRI are commonly used for screening of head-neck tumors and have been widely applied in clinical practice. Ultrasound is a simple and cost-effective tool that helps determine tumor location, size, blood flow, and internal echo. CT and MRI are superior for assessing tumor size, extent, and its relationship with surrounding tissues and nerves, with MRI providing clearer images for soft tissue evaluation. Ultrasonographically, SCSG typically appears as a heterogeneous hypoechoic mass, either solid or cystic-solid, with clear boundaries and no significant blood flow signals [41]. On CT scan, SCSG mostly exhibits roundish slightly hypodense lesions with clear boundaries, and uneven enhancement, and the surrounding muscle and bone tissues may be involved in SC in the parotid or submandibular gland [42, 43]. MRI scans typically show SCSG as oval or nodular cystic-solid masses, sometimes with convex papillary projections. The cystic component exhibits high signals on both T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI), while the solid component shows high signals on T1WI and medium to low signals on T2WI, which can be a characteristic imaging feature of SCSG [44]. In our study, cervical ultrasound revealed hyperechoic solid nodules with clear boundaries in nine cases and cystic-solid nodules in four cases, with no significant blood flow signals, suggesting a low-grade tumor. Nine cases underwent CT scan, of which eight cases had clear boundaries and one case exhibited an irregular mass in the submandibular gland with unclear boundaries, invading the mandible and the surrounding soft tissues; uneven and obvious enhancement was found in six cases, and mild enhancement in three cases. MRI scans were performed in three cases, with two showing oval solid tumors with high signals on T1WI and low signals on T2WI, and one case with a cystic component featuring nodular septation and high signals on both T1WI and T2WI. Preoperative imaging suggested malignant potential in seven cases, but failed to accurately diagnose SC.

Prior to the fourth edition of the WHO Classification of Head and Neck Tumors, SCSG was mostly classified as other types of tumors, especially zymogen granule-poor AciCC, due to its similar histological morphology and structural patterns to other salivary gland tumors (AciCC, ACC, and MEC). Therefore, SCSG should be differentially diagnosed from AciCC first [45]. AciCC lacks nodular structures with distinct fibrous septation and contains PAS-positive zymogen-like granules, which are absent in SCSG, allowing for differentiation between the two [46]. In addition, AciCC has a diversity of tumor cells, including serous alveoli, intercalated duct-like cells, and clear cells. IHC markers are crucial for the differential diagnosis of SCSG. SCSG is typically positive for S-100, mammaglobin, CK7, and MUC4, whereas Dog-1 is usually not expressed or only limited around the cancer nest. On the contrary, AciCC is usually negative for S-100 and mammaglobin but strongly positive for Dog-1 [47]. Recent studies have shown that MUC4 is moderately to strongly expressed in over 90% of SCSG cases, making it a sensitive and specific marker for SCSG diagnosis, whereas MUC4 is negative in AciCC [48]. While a combination of different IHC markers enhanced the sensitivity of SCSG diagnosis, it lacked specificity, making FISH the gold standard for SCSG diagnosis [49]. Nowadays, increasingly more retrospective studies also confirmed the ability of histomorphometric features and

Table 4 A review of the current literature on secretory carcinoma of salivary glands

Author	Patients	Gender	Age	Location	Tumor size(cm)	T1/T2/T3/T4/Tx	N0/N1/N2/N3	M0/M1	Immunohisto-chemistry
Sun J et al. (2021)	23	Male 13(56.5%) Female1(43.5%)	45 (10–69)	Parotid gland21(91.3%) Submandibular gland 2(8.7%)	2.6 (0.8–4.8)	6/14/3/0/0	18/1/4/0	21/2	S-100/MMG/CK7/ GATA3 (+);Cal-ponin/P63/DOG1 (-)
Serrano-Meneses GJ et al. (2024)	1	Male	11	Left maxillary soft tissue	5	T3N0M0			AE1-3/CK7/ GATA3/S-100(+); Actin/P63(-); Ki-67 20%
Higuchi K et al. (2014)	7	Male 3(42.9%) Female4(57.1%)	51.6 (39–68)	Parotid gland 5(71.4%) Accessory paroid 1(14.3%) Submandibular gland 1(14.3%)	1.8 (0.8–3.5)	7/0/0/0/0	7/0/0/0	7/0	S-100/MMG/ vimentin/MUC1(+); Ki-67 7.8%(5-12.5%)
Min FH et al. (2021)	1	Male	32	Parotid gland	2	T1N0M0			S-100/MMG/ CK5/6/7/8/Vim/ SMA/p63(+); DOG1/calponin(-); Ki-67 2%
Salgado CM et al. (2021)	4	Male 2 (50%) Female2(50%)	11 (7–14)	Parotid gland3(75%) Submandibular gland1(25%)	1.5 (1.2–2.1)	3/1/0/0/0	4/0/0/0	4/0	S-100/MMG/CK7/ GATA3(+); CK5/6/p53(-); Ki-67 20–30%
Baněčková M et al. (2023)	215	Male123(57.2%) Female8(40.5%) Unknow 5(2.3%)	47.5 (7–94)	Parotid gland 159(74%) Submandibular gland 14(6.5%) Lip 12(5.6%) Buccal mucosa 10 (4.7%) Palate 10 (4.7%) Oral cavity 5 (2.3) Sinonasal tract 5 (2.3)	1.98 (4–70)	129/48/6/7/25	97/10/10/98	120/6	S-100(+) 206/206 MMG(+) 195/197 DOG1(-) 127/147 NOR1(-) 73/73 p63(-) 152/178
Kim SH et al. (2019)	1	Male	40	Parotid gland	3.9	T3N0M0			EMA/ Vimentin/S-100(+); p63/CK5/6/C-KIT(-)
Wu B et al. (2020)	1	Male	72	Left nasal cavity	0.8	T1N0M0			S-100/MMG/ GATA3(+); p63/DOG1(+); Ki-67 10%
Langah NA et al. (2023)	1	Male	42	Minor salivary glands	2.3	T1N2bMx			GATA3/MUC4(+); AR(-)
Xu B et al. (2017)	1	Male	61	Maxillary sinus	4.2	T3N0M0			CK7/S-100/MMG/ GCDFP-15(+)
Sun L et al. (2019)	1	Male	57	Parotid gland	1.6	T1N0M0			α-1-anti-trypsin/ MMG/S-100(+); AR/BRST-2/CK20/ P63/SM(-); Ki-67 5–10%
Boliere C et al. (2019)	1	Male	57	Minor salivary glands	1.0	T4N0M0			CK7/SM/P53/CK5/6/ MMG/S-100(+); DOG-1(-)

Table 4 (continued)

Author	Patients	Gender	Age	Location	Tumor size(cm)	T1/T2/T3/T4/Tx	N0/N1/N2/N3	M0/M1	Immunohisto-chemistry
Martínez R et al. (2019)	1	Female	23	Minor salivary glands	2.0	T4N1M0			AE1/3/S-100/MMG/ GATA3(+); DOG1/p63(-); Ki-67 20%
Cai Y et al. (2019)	5	Male 5(100%)	46 (34–60)	Parotid gland	2.72 (2-3.5)	1/3/1/0/0	5/0/0/0	4/1	S-100/MMG/ Vimentin/CK(+); p63(-); Ki-67 10%
Gonzalez MF et al. (2017)	1	Male	18	Parotid gland	2.7	T2N0M0			MMG/S-100/ SOX-10/MUC-1/4/p63(focal)/ GCDFP-15(+)
Anderson JL et al. (2019)	55	Male 31(56.4%) Female24(43.6%)	48.6 (12–82)	Parotid gland 42(76.4%) Submandibular gland 3(5.5%) Major salivary gland 10(18.2%)	1.95	27/19/3/1/5	51/3/1	55/0	-
Ngouajio AL et al. (2017)	12	Male 6(50%) Female6(50%)	15 (10–17)	Parotid gland 10(83%) Submandibular gland 1(8.5%) Lip 1(8.5%)	2.41 (1-3.8)	3/6/1/0/2	11/1/0/0	12/0	S-100(+) 11(100%) Vimentin(+) 4 CK19(+) 3 MMG(+) 2
Rooper LM et al. (2018)	1	Female	59	Submandibular gland	4.7	T3N2M0			S-100/MMG/p63(+); DOG-1/SOX10(-)
Hsieh MS et al. (2015)	14	Male 8 (57%) Female6 (43%)	32.5 (17–55)	-	2.5 (1.2–4.5)	5/6/3/0/0	11/2/1/0	-	S-100/MMG/ Vimentin(+); DOG1(93%)(-)
E.Boon et al. (2018)	31	Male17(55%) Female14(45%)	49 (19–83)	Parotid gland 18(58%) Submandibular gland 1(3%) Minor salivary glands 12(39%)	-	19/10/0/0/2	30/0/1/0	31/0	-
Bacem A et al. (2017)	279	Male 167(60%) Female 112(40%)	45.68	Parotid gland 189(68%) Buccal mucosa 24(9%) Submandibular gland 22(8%) Lip 25 (9%) Hard palate 12 (4%) Soft palate 6(2%) Base of the tongue 1 (0)	1.8	-	-	-	-
Din NU et al. (2016)	11	Male 7(63.6%) Female 5(36.4%)	27.5 (9–60)	Parotid gland 7 Submandibular gland 3 Buccal vestibule 1	4.4 (2–10)	-	-	-	S-100(+) 5/5 EMA(+) 4/4 CK7(+) 2/2

IHC markers to diagnose more than 95% of cases, and significantly reduce the need for molecular detection, thereby saving healthcare resources. Moreover, genetic analysis can be still carried out for very few atypical cases [50–52]. In our study, HE staining revealed lobulated or nodular cell arrangements in six cases, with mammillary structures and luminal secretion in some areas. At high magnification, the cells appeared relatively uniform

in size, round or oval in shape, with mild atypia. The nuclear membrane was distinct, small nucleoli were visible, and the cells exhibited low-grade atypia with abundant cytoplasm. Immunohistochemistry revealed strong positivity for Mammaglobin and S-100, and negativity for Dog-1. Based on these typical cytological and immunohistochemical features, a diagnosis of SC was made without further FISH testing. Seven cases underwent FISH, with some showing larger and more atypical tumor cells arranged in solid sheets. Two cases were negative for mammaglobin, with one case was also negative for MUC4. Preliminarily, AciCC was not excluded, and genetic testing was further performed to achieve accurate diagnosis, typical ETV6-NTRK3 fusion was detected, so it was diagnosed with SC. Therefore, FISH is necessary when the cells microscopically have an atypical morphology, high atypia, and prominent nucleoli, and IHC for mammaglobin, S-100, and Dog-1 does not verify the diagnosis.

During the development of SCSG, high-grade transformation may occur in a small number of patients, where the tumor loses its differentiation potential and becomes more aggressive [53, 54]. In high-grade transformation, SCSG typically exhibits infiltrative growth, with tumor cells arranged in solid, glandular, or trabecular structures, accompanied by single-cell infiltration, increased cell atypia, thickened nuclear chromatin, more frequent mitoses, and necrosis. Invasion of surrounding soft tissues and nerves is also more common [53–55]. In our study, none of patients developed high-grade transformation, which was probably attributed to the small sample size.

Similar to mammary SC, SCSG is usually characterized by a characteristic t(12;15)(p13;q25) translocation, resulting in the ETV6-NTRK3 gene fusion, which is unique among salivary gland tumors [56]. ETV6-NTRK3 gene fusion has also been reported in other non-salivary gland tumors, such as infantile fibrosarcoma, acute myeloid leukemia, inflammatory myofibroblastoma, and cellular congenital mesodermal nephroma [57]. With the growing understanding of SCSG, it has been discovered that besides NTRK3, RET [58], MET [59], and MAML3 [60] are also the ETV6 fusion partners in SCSG. In 2020, Black M [43] reported an even rarer case of double-gene fusion (ETV6-RET and EGFR-SEPT14), further expanding the molecular spectrum of SC. In our study, seven cases were tested for the ETV6 gene and they were all positive, with no gene fusions other than ETV6-NTRK3 detected.

According to the American Society of Clinical Oncology (ASCO) guidelines, SCSG is classified as a low-invasive salivary gland carcinoma, and, similar to other salivary gland tumors, radical excision is the treatment of choice [61–63]. Relevant studies suggest that about 70% of SCSG is in the early stage with a less than 20% regional lymph node metastasis rate at the time of diagnosis, so simultaneous cervical lymph node dissection and postoperative adjuvant radiotherapy and chemotherapy are not required for SCSG [8, 64, 65]. Postoperative comprehensive antitumor therapies such as radiotherapy, chemotherapy, and targeted therapy are recommended for SCSG with high-risk factors, such as positive lymph node metastasis, vascular invasion, positive margins, and positive peripheral neuromuscular invasion [62, 65, 66]. Although SCSG is a low-grade malignancy, high-grade transformation can occur in a few patients, resulting in significantly higher malignancy and a high rate of cervical lymph node metastasis. In such cases, sialoadenectomy and cervical lymph node dissection with adjuvant chemoradiotherapy are recommended [53]. Targeted therapy with tropomyosin receptor kinase (TRK) inhibitors may also be considered for patients with typical gene fusion (ETV6-NTRK3) [67]. The prognosis for patients with typical SCSG is generally favorable, with a disease-specific survival rate of about 95-98% and disease-free survival of about 87-89% following radical excision [14, 15]. However, patients with high-grade transformation tend to have a poorer prognosis, with survival typically ranging from 2 to 6 years postoperatively [68]. Genetic testing and targeted therapy should be considered for advanced patients with recurrent, metastatic, or inoperable tumors [69]. In our study, cervical lymph node dissection was performed in seven cases, with pathological detection of cervical lymph node metastasis in two cases. One of these cases involved invasion of surrounding soft tissues and the mandible, as well as one case of invasion into the facial nerve. Therefore, attention should be paid to the regional lymph nodes in the face of large tumors or high-risk factors such as surrounding tissue invasion, and cervical lymph node dissection can be performed when necessarily. In our study, during follow-up, two patients experienced tumor recurrence at the surgical site, with one of them also developing cervical lymph node metastasis. Both of these patients had undergone superficial parotidectomy along with tumor resection during their initial surgery, and postoperative pathological examination showed Ki-67 positive rate was 10% and 15%, respectively. However, no recurrences were observed in patients who underwent total parotidectomy. Based on these findings, we hypothesize that a high Ki-67 index and partial parotidectomy may be associated with local recurrence in our study. It's also suggest that preoperative assessment of the tumor's nature, size, and extent is crucial for selecting the appropriate surgical plan and comprehensive treatment. Radical excision and regional lymph node dissection may be one of the effective means for reducing the relapse rate in patients with associated high-risk factors. In our study, one patient died of acute myocardial

infarction, and no relapse was detected by imaging during follow-up.

In conclusion, SCSG is a rare low-grade malignancy with a good prognosis. Pathological and IHC characteristics are the key to SC diagnosis, and ETV6 translocation is considered the gold standard for its diagnosis. Surgical excision is the primary treatment for SCSG, and whether to perform simultaneous cervical lymph node dissection and other adjuvant therapies should be determined based on the pathological stage and the presence or absence of high-risk factors.

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Author contributions
All authors contributed to the study conception and design. Writing - original draft preparation: [Fei Han, Feng Liu, Xinrong Nan]; Writing - review and editing: [Fei Han, Hao Wang, Xuesong Wu]; Conceptualization: [Feng Liu, Yanchao Qin, Zhen Guo]; Methodology: [Fei Han, Qian Lu]; Formal analysis and investigation: [Feng Liu, Qian Lu, Zhen Guo]; Resources: [Xinrong Nan, Yanchao Qin, Zhen Guo]; Supervision: [Xinrong Nan, Fei Han], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has received approval from our institution's ethics committee (Ethics number: KY2024054), and informed consent has been duly obtained from both the patients and their families.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Skálová 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(5):599–608.
2. Seethala RR, Stenman G. Update from the 4th edition of the World Health Organization classification of head and neck tumours: tumors of the salivary gland. Head Neck Pathol. 2017;11(1):55–67.
3. Sun J, Liu S, Fu K, et al. Clinicopathological characteristics and outcomes of 23 patients with secretory carcinoma of major salivary glands. Sci Rep. 2021;11(1):22639.
4. Suzuki K, Harada H, Takeda M, et al. Clinicopathological investigation of secretory carcinoma cases including a successful treatment outcome using entrectinib for high-grade transformation: a case report. BMC Med Genomics. 2022;15(1):6.
5. Skálová A, Hyrcza MD, Leivo I. Update from the 5th edition of the World Health Organization classification of head and neck tumors: salivary glands. Head Neck Pathol. 2022;16(1):40–53.
6. Forsythe A, Zhang W, Phillip Strauss U, et al. A systematic review and meta-analysis of neurotrophic tyrosine receptor kinase gene fusion frequencies in solid tumors. Ther Adv Med Oncol. 2020;12:1758835920975613.
7. Miesbauerová M, Tommola S, Šteiner P, et al. Cytopathological features of secretory carcinoma of salivary glands and ancillary techniques in its diagnostics: impact of new Milan system for reporting salivary gland cytopathology. Apmis. 2019;127(7):491–502.
8. Boliere 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;2019:7416302.
9. Mossinelli C, Pigni C, Sovardi F, et al. Synchronous parotid (Mammary analog) secretory carcinoma and acinic cell carcinoma: report of a case. Head Neck Pathol. 2019;13(4):686–91.
10. Jackson BS, Pratt TL, Van Rooyen A. Mammary analogue secretory carcinoma: a rare salivary gland tumour. S Afr Med J. 2017;107(4):304–6.
11. Min FH, Li J, Tao BQ, et al. Parotid mammary analogue secretory carcinoma: a case report and review of literature. World J Clin Cases. 2021;9(16):4052–62.
12. Ngouajio AL, Drejet SM, Phillips DR, et al. A systematic review including an additional pediatric case report: pediatric cases of mammary analogue secretory carcinoma. Int J Pediatr Otorhinolaryngol. 2017;100:187–93.
13. Salgado CM, Alaggio R, Reyes-Múgica M, et al. Clinicopathologic and molecular characterization of four cases of pediatric salivary secretory carcinoma (SSC), one with ETV6-RET fusion. Head Neck Pathol. 2021;15(3):796–802.
14. Baněčková M, Thompson LDR, Hyrcza MD, et al. Salivary gland secretory carcinoma: clinicopathologic and genetic characteristics of 215 cases and proposal for a grading system. Am J Surg Pathol. 2023;47(6):661–77.
15. Xu B, Viswanathan K, Umrau K, et al. Secretory carcinoma of the salivary gland: a multi-institutional clinicopathologic study of 90 cases with emphasis on grading and prognostic factors. Histopathology. 2022;81(5):670–9.
16. Wiles AB, Gabrielson M, Baloch ZW, et al. Secretory carcinoma of the salivary gland, a rare entity: an international multi-institutional study. Cancer Cytopathol. 2022;130(9):684–94.
17. Serrano-Meneses GJ, Brenes Guzmán S, Serrano-Meneses MA, et al. Insights into pediatric secretory carcinoma of the salivary gland: a case report. Cureus. 2024;16(5):e60355.
18. de Lima-Souza RA, Ferreira IV, Chone CT, et al. Secretory carcinoma of the minor salivary gland: an in-depth case report. Oral Oncol. 2024;158:107005.
19. Sakhariya SV, Chincholkar A, Tidke S, et al. Unmasking the rarity of mammary analogue secretory carcinoma of the minor salivary gland - a case report. Int J Surg case Rep. 2024;124:110374.
20. Chu YH, Kobrossy B, Schwartz D, et al. Secretory carcinoma of the thyroid: a case report and update of literature. Head Neck Pathol. 2024;18(1):84.
21. Mahomed F, de Bruin J, Ngwenya S, et al. ETV6 molecular heterogeneity in salivary secretory carcinoma: a case series report and literature review. Head Neck Pathol. 2024;18(1):66.
22. Duraisamy KG, C S. Non indigenous mammary secretory carcinoma of parotid gland - an unusual presentation. Indian J Otolaryngol head neck Surgery: Official Publication Association Otolaryngologists India. 2024;76(3):2859–68.
23. Mokhles P, Sadeghipour A, Babaheidarian P, et al. Salivary gland secretory carcinoma presenting as a cervical soft tissue mass: a case report. J Med Case Rep. 2024;18(1):78.
24. Wang T, Yang X, Yao L, et al. Clinicopathological analysis of 18 cases of secretory carcinoma of the salivary glands. J Dent Sci. 2024;19(1):109–17.
25. Patel A, LaBarge B, King TS, et al. Defining the clinical characteristics of mammary analog secretory carcinoma of the salivary gland: analysis of the national cancer database. SAGE open Med. 2023;11:20503121231200103.
26. Moriyama E, Nagasu S, Tanaka T, et al. Case report: a case of complete response to entrectinib in NTRK fusion gene-positive parotid gland cancer. Front Oncol. 2023;13:1247435.
27. Langah NA, Ahad A, Ghaloo SK, et al. Secretory carcinoma of minor salivary glands of buccal mucosa: a case report and review of the literature. Int J Surg case Rep. 2023;107:108357.
28. Bhandarkar AM, Menon A, Geetha V, et al. Mammary analogue secretory carcinoma of parotid - a pathological mystery. Indian J Otolaryngol head neck Surgery: Official Publication Association Otolaryngologists India. 2023;75(2):905–8.
29. Ash J, Mallick S, Vogiatzis P, et al. Secretory carcinoma in the parotid gland of a pediatric patient. A challenging diagnosis. J oral Maxillofacial Pathology: JOMFP. 2023;27(2):420–3.
30. Avondet L, Adan R, Berenstein BM, et al. Mammary analogue secretory carcinoma of the salivary glands. Ecancermedicalscience. 2023;17:1511.

31. Lassche G, van Engen-van Grunsven ACH, van Hooij O, et al. Precision oncology using organoids of a secretory carcinoma of the salivary gland treated with TRK-inhibitors. Oral Oncol. 2023;137:106297.
32. Yue C, Zhao X, Ma D, et al. Secretory carcinoma of the sinonasal cavity and pharynx: a retrospective analysis of four cases and literature review. Annals Diagn Pathol. 2022;61:152052.
33. Saliba M, Mohanty AS, Ho AL, et al. Secretory carcinoma of the thyroid in a 49-year-old man treated with larotrectinib: protracted clinical course of disease despite the high-grade histologic features. Head Neck Pathol. 2022;16(2):612–20.
34. Yassin-Kassab A, Gainor D, Sufyan AS. Atypical presentation of mammary analogue secretory carcinoma of the lip. Ear Nose Throat J. 2022;101(5):Np212–7.
35. Ogawa M, Yokoo S, Yamaguchi T, et al. Diagnosis and treatment of secretory carcinoma arising from the oral minor salivary gland: two case reports. Medicine. 2021;100(51):e28390.
36. Agaimy A, Baněčková M, Ihrler S, et al. ALK rearrangements characterize 2 distinct types of salivary gland carcinomas: clinicopathologic and molecular analysis of 4 cases and literature review. Am J Surg Pathol. 2021;45(9):1166–78.
37. 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(3):893–904.
38. Vasanthi V, Ramadoss R. Secretory carcinoma of salivary gland - a systematic review of pediatric case reports and case series. J oral Maxillofacial Pathology: JOMFP. 2021;25(2):327–31.
39. Owosho AA, Tyler D, Summersgill KF. A clinicopathologic study of secretory carcinoma of minor salivary gland: a series of 4 cases and diagnostic considerations. Oral Surg oral Med oral Pathol oral Radiol. 2021;131(4):463–7.
40. Nakaguro M, Faquin WC, Baloch ZW, et al. Fine needle aspiration of salivary gland carcinomas with high-grade transformation: a multi-institutional study of 22 cases and review of the literature. Cancer Cytopathol. 2021;129(4):318–25.
41. Terada T, Kawata R, Noro K, et al. Clinical characteristics of acinic cell carcinoma and secretory carcinoma of the parotid gland. Eur Arch Otorhinolaryngol. 2019;276(12):3461–6.
42. Tokuzen N, Goda H, Nakashiro K. Locally advanced mammary analogue secretory carcinoma of the parotid gland. Int J Oral Maxillofac Surg. 2019;48(7):865–8.
43. Black M, Liu CZ, Onozato M, et al. Concurrent identification of novel EGFR-SEPT14 fusion and ETV6-RET fusion in secretory carcinoma of the salivary gland. Head Neck Pathol. 2020;14(3):817–21.
44. Kim SH, Hong ME, Lee DJ. A case of mammary analogue secretory carcinoma of the parotid gland: a case report. Med (Baltim). 2020;99(28):e20218.
45. 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(4):419–26.
46. 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(4):531–40.
47. Khurram SA, Speight PM. Characterisation of DOG-1 expression in salivary gland tumours and comparison with myoepithelial markers. Head Neck Pathol. 2019;13(2):140–8.
48. Taverna C, Baněčková M, Lorenzon M, et al. MUC4 is a valuable marker for distinguishing secretory carcinoma of the salivary glands from its mimics. Histopathology. 2021;79(3):315–24.
49. Wu B, Loh TKS, Vanecek T, et al. (Mammary analogue) Secretory carcinoma of the nasal cavity: report of a rare case with p63 and DOG1 expression and uncommon exon 4-Exon 14 ETV6-NTRK3 Fusion diagnosed with next generation sequencing. Head Neck Pathol. 2020;14(2):542–9.
50. Pang Y, Sun L, Liu H, et al. Differential diagnosis and treatment of salivary secretory carcinoma and acinic cell carcinoma. Oral Oncol. 2021;119:105370.
51. Hamamoto Y, Harada H, Kohara M, et al. Usefulness of immunohistochemistry to distinguish between secretory carcinoma and acinic cell carcinoma in the salivary gland. Med Mol Morphol. 2021;54(1):23–30.
52. 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.
53. 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(3):107–18.
54. 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(10):1295–307.
55. Xu B, Aryeequaye R, Wang L, et al. Sinonasal secretory carcinoma of salivary gland with high grade transformation: a case report of this under-recognized diagnostic entity with prognostic and therapeutic implications. Head Neck Pathol. 2018;12(2):274–8.
56. Sharma P, Sivakumar N, Pandiar D. Diagnostic accuracy of pan-TRK immunohistochemistry in differentiating secretory carcinoma from acinic cell carcinoma of salivary gland-A systematic review. J Oral Pathol Med. 2023;52(3):255–62.
57. Gatalica Z, Xiu J, Swensen J, et al. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019;32(1):147–53.
58. Skalova A, Vanecek T, Martinek P, et al. Molecular profiling of mammary analog secretory carcinoma revealed a subset of tumors harboring a novel ETV6-RET translocation: report of 10 cases. Am J Surg Pathol. 2018;42(2):234–46.
59. Rooper LM, Karantanos T, Ning Y, et al. Salivary secretory carcinoma with a novel ETV6-MET fusion: expanding the molecular spectrum of a recently described entity. Am J Surg Pathol. 2018;42(8):1121–6.
60. Guilmette J, Dias-Santagata D, Nosé V, et al. Novel gene fusions in secretory carcinoma of the salivary glands: enlarging the ETV6 family. Hum Pathol. 2019;83:50–8.
61. Pfister DG, Spencer S, Adelstein D, et al. Head and neck cancers, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18(7):873–98.
62. Ayre G, Hyrcza M, Wu J, et al. Secretory carcinoma of the major salivary gland: Provincial population-based analysis of clinical behavior and outcomes. Head Neck. 2019;41(5):1227–36.
63. Sun L, Thorson T, Zhu R, et al. A case report of parotid mammary analogue secretory carcinoma and reviews. Int J Surg Case Rep. 2019;55:88–91.
64. Anderson JL, Haidar YM, Armstrong WB, et al. Analysis of clinical features of Mammary Analog Secretory Carcinoma using the Surveillance, Epidemiology, and end results database. JAMA Otolaryngol Head Neck Surg. 2019;145(1):91–3.
65. Martínez R, Marín C, Niklander S, et al. Exophytic swelling of the buccal mucosa in a young female patient. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(4):267–71.
66. Cai Y, Cai F, Qiao H, et al. The significance of the morphological and immunological characteristics in the diagnosis of parotid mammary analogue secretory carcinoma: five case reports and a review of the literature. Int J Clin Exp Pathol. 2019;12(6):2233–40.
67. 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(8):731–9.
68. Cipriani NA, Blair EA, Finkle J, et al. Salivary gland secretory carcinoma with high-grade transformation, CDKN2A/B loss, distant metastasis, and lack of sustained response to crizotinib. Int J Surg Pathol. 2017;25(7):613–8.
69. 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. 2021;132(4):e143–52.

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