

## Original Article

# Mammary analogue secretory carcinoma of the minor salivary gland: report of two cases

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**Abstract:** Mammary analogue secretory carcinoma (MASC) is a recently described salivary gland tumour notable for a balanced chromosomal translocation t(12;15)(p13;q25) that contributes to ETV6 gene rearrangements. It was first reported in 2010 by Skalova et al. with histological features resembling secretory carcinoma of the breast and was acknowledged and referred to as “secretory carcinoma” in the updated 2017 WHO classification. It is reported that MASC accounts for <0.3% of all salivary gland tumours, with a finite number of published reports on it. MASC has a range of histological features and clinical behaviours. The histopathological diagnosis of MASC can be difficult with current immunohistochemical methods. One case was located in the left palate, and 1 case was located in the soft palate. The maximum diameter of the tumour was 1.4~3.7 cm. CT demonstrated a mass that had not invaded into the palate bone, and the patients underwent palate neoplasm expanded ectomy without neck dissection or postoperative radiation therapy. Histopathological examination revealed that the tumour cells consisted of a mixed arrangement of microcystic, papillary-cystic, follicular, and solid lobular growth patterns. Eosinophilic cytoplasm and intraluminal or intracytoplasmic colloid-like secretions were observed. The final pathology confirmed the diagnosis of MASC with immunohistochemically neoplastic cells staining positive for S-100 and mammaglobin. The patients were asymptomatic at their 12-month follow up. More studies are needed to identify the typical behaviour of this tumour and establish the standard treatment regimen. This study aims to reinforce the awareness of this tumour by analysing its clinicopathologic features, immunophenotype, and diagnosis.

**Keywords:** Mammary analogue secretory carcinoma, clinical feature, diagnosis, treatments, prognosis

## Introduction

Mammary analogue secretory carcinoma (MASC) of salivary glands is an exceedingly rare low-grade malignant tumour that has similarity with secretory carcinoma of the breast and was originally reported by Skálová et al. in 2010 [1, 2]. MASC is notable for a fusion of the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15 with translocation t(12;15)(p13;q25), harbouring ETV6-NTRK3, and in rare cases ETV6-RET fusion in fluorescence in situ hybridization (FISH) [3, 4].

Clinically, the tumour has a typical presence of solid, painless, and slow-growing nodules that are sometimes poorly differentiated or locally fixed. MASC tumours prevalingly occur in the major salivary glands, predominantly in the parotid, posterior in the submandibular gland

and in the oral cavity (soft palate, buccal mucosa, and lip) [5, 6].

Pathologically, it closely resembles secretory carcinoma of the breast, composed of bland cells with an eosinophilic vacuolated cytoplasm, round nuclei (which are arranged in tubules), micro- or macro-cysts and papillae, with the absence of zymogen granules in acinic cell carcinoma [7]. The diagnosis and differential diagnosis of MASC from other salivary gland tumours are based on histological features, immunohistochemistry, and genetic examination, which are positive for mammaglobin, S-100 protein, and PAS-diastase but negative for DOG-1 [8].

In this report, we present two cases of a MASC of minor salivary gland (the palate) tissue in two young and middle-aged women, presenting



**Figure 1.** Neck CT with contrast was performed. An approximately 3.0-cm mass (white arrow) in the hard palate on the left side was noted. No palate extension was seen.

without bone destruction or cervical lymph node metastasis. To our knowledge, only eighteen cases of MASC of the palate have been published in the literature worldwide to date, including twelve on the hard palate and six on the soft palate [9]. We describe an additional case involving the clinical course, presentation, and immunohistological findings with a brief review of the literature.

## Materials and methods

### General information

The clinical data of 2 cases of minor salivary gland MASC treated in our hospital in 2018 were selected. The 2 cases were females, aged 50 and 34 years old, both with MASC located in the palate. Both cases were followed up for 12 months, and no recurrence or metastasis was found.

### Method

The EnVision two-step method was used for immunohistochemical staining. Primary antibodies against S-100 protein, mammaglobin, CK7, vimentin, DOG1, P63, SMA, and Ki67 were used. The staining was carried out according to the antibody instructions, and negative

and positive controls were routinely prepared. S-100 positive staining was defined as the simultaneous staining of the nucleus and cytoplasm, SMA positive staining was defined as cytoplasmic staining, and DOG1 positive staining was defined as cell membrane colouring. The location, size, boundary, colour and texture of the tumour were recorded. The tumour boundary, histological configuration, cytological characteristics and stroma were observed under a microscope. Characteristics and other accompanying characteristics were noted.

## Results

### Gross examination

The tumour was a gross, regular-border lesion mass, without evidence of frank tumour extension into the palate (**Figure 1**). The maximum diameter of the tumour was 1.4~3.7 cm. The gross resected specimen was well-circumscribed and grass-green in colour and showed cystic lobular nodules on the surface. The section was greyish yellow and greyish brown.

### Pathological changes

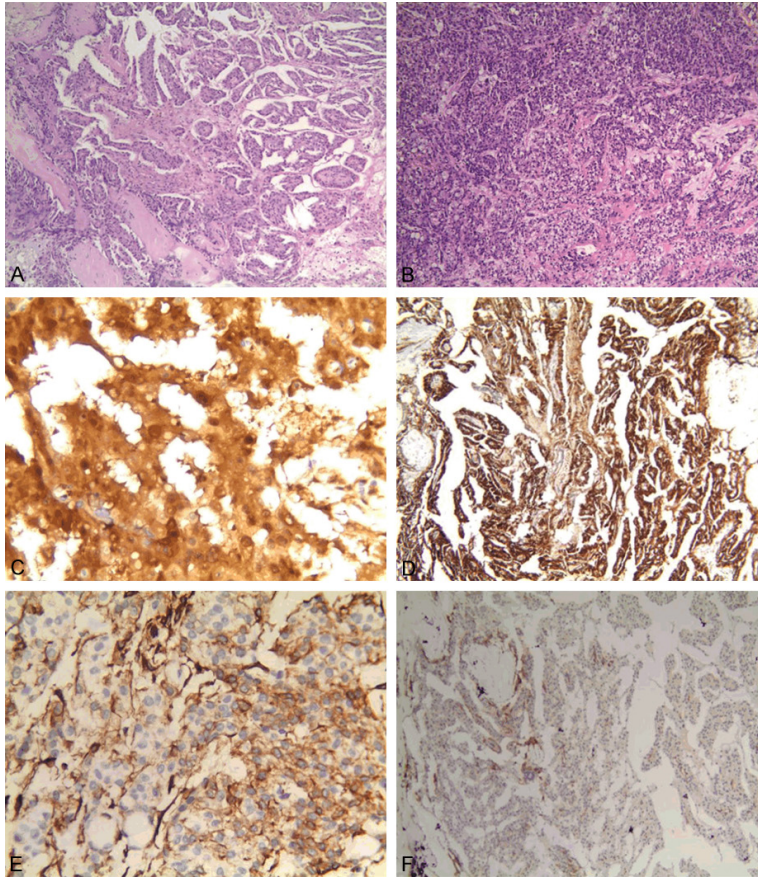
The tumour was arranged in various growth patterns, including tubular, papillary-cystic, cystic and solid architectural patterns. The tumour lobules were divided by fibrous septa, and homogenous eosinophilic secretions were seen. The tumour cells were well-circumscribed, small to medium in size, showed round to oval nuclei and had an abundant granular eosinophilic cytoplasm within vacuolating changes and a lack of basophilic coarse zymogen granules. Mild nuclear atypia was seen, but mitoses were very rare.

### Immunohistochemical findings

The neoplastic cells showed positive staining for S-100, mammaglobin and vimentin and negative staining for DOG1, P63, SMA, and CK7 (**Figure 2**). The proliferation rate as assessed by Ki-67 was below 10%. Pathological and immunohistochemical features should be comprehensively considered for the diagnosis of MASC.

The diagnostic result, in which the cytological and immunohistochemical staining profiles were systematically considered, was MASC

## Mammary analogue secretory carcinoma of the minor salivary gland



**Figure 2.** Mammary analogue secretory carcinoma of the salivary gland histologic features (Haematoxylin-eosin staining). (A) shows the papillary architecture (magnification  $\times 200$ ). (B) shows the solid architecture (magnification  $\times 200$ ). Immunohistochemistry for mammary analogue secretory carcinoma. The tumour cells are positive for S-100 (C), mammaglobin (D), and vimentin (E) and are negative for DOG-1 (F) (magnification  $\times 200$ ).

involving the minor salivary gland with no invasion of the palate bone. The patients were asymptomatic, had no recurrence, node involvement, or distant metastases at their 12-month follow-up without postoperative radiation therapy.

### Discussion

Mammary analogue secretory carcinoma was first named on account of its notable morphologic, immunohistochemical, and molecular resemblance to secretory carcinoma of the breast and occasionally occurs in the skin and lung [1, 10]. Skalova et al. described 16 cases that were previously reported as adenocarcinoma/cystadenocarcinoma not otherwise specified (NOS). Both tumour types demonstrate a t(12;15) translocation involving the ETS variant

6 (ETV6) gene on chromosome 12 and the neurotrophic tyrosine kinase receptor type 3 (NTRK3) gene on chromosome 15, but few are reported to be negative. Since then, new reports on mammary analogue secretory carcinoma have been increasing gradually, and the related research has also increased.

According to statistics, MASC accounts for approximately 4% of malignant salivary gland tumours, and there are approximately three hundred cases reported to date. The age of the reported cases ranges from 9 to 77, concentrated in those 50 years of age, with few cases in children and adolescents [11]. A slight male majority was noted in most series but although the tumor occurs in men more than in women, there were no significant differences between the sexes, and no racial predispositions [12-15].

MASC mainly occurs in the parotid gland, but it can also arise in the submandibular gland or small salivary glands

and other accessory parotid glands. Of all reported cases in the oral cavity, the parotid gland accounted for approximately 70% and the cheek 8%, with the palate, skin, lung, base of the tongue and lip accounting for fewer cases [8-15]. The diameter of the tumour varies from 0.2 cm to 8.5 cm. The duration of the symptoms ranged from 2 months to 30 years [16]. Among the reported cases in the current study, there was a regional difference in different areas, in which North America showed an apparently higher percentage than other continents, and Africa and South America reported hardly any cases [12]. Generally, MASC is a low-grade malignant disease with low postoperative metastasis and a high survival rate [17]. MASC is mainly identified with salivary acinic cell carcinoma (AciCC), mucoepidermoid carcinoma (MEC), cystadenocarcinoma, or other

## Mammary analogue secretory carcinoma of the minor salivary gland

salivary gland tumours that show parallel clinical, histologic and immunohistochemical features [18-20] as MASC. However, the morphology, IHC, and molecular findings help distinguish between these tumours and MASC [21].

In immunohistochemical staining, MASC was positive for mammaglobin, S-100, STAT5a, waveform protein, GCDFP-15, AE1/AE3, EMA, broad-spectrum cell keratins (CK7, CK8, CK18, CK19), and epithelial membrane antigen. MASC was negative for DOG-1, CK5/6, CK14, and SMA [22, 23]. Among these antigens, the diagnostic sensitivity of mammaglobin and S-100 is as high as 95% [24] in establishing the cytological diagnosis of MASC, but this information needs to be combined with supportive clinicopathological traits. S-100 can also be expressed positively in certain low-grade epithelial-derived tumours, such as polymorphous low-grade adenocarcinoma (PLGA) and low-grade salivary duct carcinoma (LGSDC) [25].

Therefore, MASC must be excluded before diagnosing adenocarcinoma or cystic adenocarcinoma. The chromosomal alteration may be detected by break-apart ETV6 fluorescence in situ hybridization (FISH) or by detecting the ETV6-NTRK3 fusion transcript by reverse transcription-polymerase chain reaction (RT-PCR), which is currently the gold standard for diagnosing MASC. However, given the highly professional nature of its test and its clinical impracticality, microscopic characteristic morphology combined with immunohistochemistry has become the basis of MASC diagnosis [26].

Further research is needed for more accurate information on the clinical behaviour and prognosis of MASC, especially for standardizing the guidelines for surgical treatment, chemoradiation, and the follow-up time. Local lymph node and distant metastasis, postoperative recurrence, and deaths associated with the disease have been found [27-29], although MASC is considered to be a low-grade malignant tumour similar to adenocarcinoma [30]. Currently, the optimal management is unknown, but surgical excision with neck dissection based on clinical, radiological, and histological features is the mainstay treatment. Therefore, we should concentrate on ETV6-NTRK3 to provide important information for more effective potential therapeutic targets for future treatment [31, 32]. The occurrence of high-level transformation

involves an increase in invasiveness and to date, there have been 4 cases reported with high-grade transformation [33, 34].

### Conclusion

In summary, MASC is a newly introduced malignant tumour of the salivary glands, and clinical manifestations, immunohistochemical staining and cytogenetic analysis provide diagnostic support for the diagnosis. The current therapeutic method is primary surgical excision and selective/radical neck dissection or radiotherapy, according to the clinic. This report aimed to improve the awareness of the diagnosis and reviewed the current opinions for this rare neoplasm. In additional cases, patients should be followed up for a longer time to guide patient care and predict outcome.

### Disclosure of conflict of interest

None.

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## Mammary analogue secretory carcinoma of the minor salivary gland

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## Mammary analogue secretory carcinoma of the minor salivary gland

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