

## Case Report

# Mammary analogue secretory carcinoma presenting as a salivary gland neoplasm: a first clinical case report of an exceptionally rare tumor in China

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Received June 17, 2016; Accepted August 22, 2016; Epub November 15, 2016; Published November 30, 2016

**Abstract:** Mammary analogue secretory carcinoma (MASC), which commonly occurs in the parotid gland, is a newly described salivary gland carcinoma that has morphologic, genetic, and immunohistochemical characteristics similar to those of secretory breast carcinoma. Previously, MASC was typically diagnosed as acinic cell carcinoma or as adenocarcinoma not otherwise specified. Making a preoperative or intraoperative diagnosis of MASC is challenging. Most studies of MASC have focused on the genetic and histologic characteristics of the tumor, and no studies have described the clinical characteristics of MASC. To the best of our knowledge, we present here the first report of the clinical management of a case of MASC in China. The new knowledge about the diagnostic, prognostic, and therapeutic implications of MASC that this report provides may help clinicians and surgeons make better decisions in the care of MASC patients.

**Keywords:** Mammary analogue secretory carcinoma, salivary gland tumors, parotid gland tumors

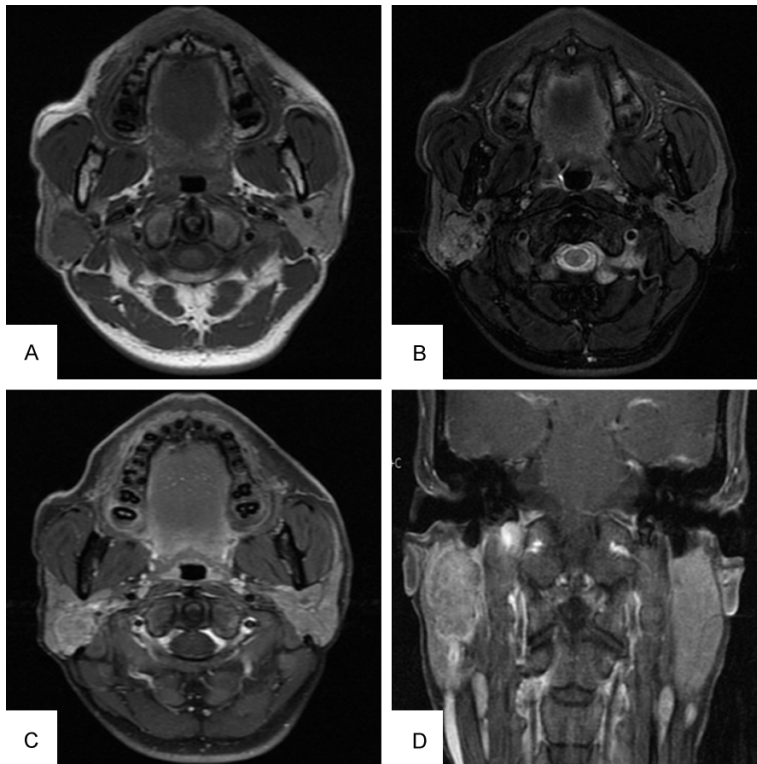
## Introduction

Mammary analogue secretory carcinoma (MASC), a rare neoplasm of the salivary glands that shares some morphologic, genetic, and immunohistochemical characteristics with secretory carcinoma of the breast, was first reported by Skalova et al. in 2010 [1]. MASC most commonly occurs in the parotid gland and can easily be mistaken for acinic cell carcinoma or for adenocarcinoma not otherwise specified [2]. The neoplasm may present at any age and occurs more frequently in men than in women. In general, the tumor has circumscribed borders but is not encapsulated; has a white-grey, brown, or yellow color; and has a prominent cystic component [1-6]. The mean size of the tumor has been reported to be 1.7 cm (range, 0.2-5.5 cm) [2].

Histologically, perineural invasion is occasionally present; lymphovascular invasion has not

been reported. Microscopically, MASC is composed of uniform cells with bland-looking vesicular nuclei and eosinophilic vacuolated cytoplasm in a tubular, microcystic solid growth pattern with abundant periodic acid-Schiff-positive secretions. Strong immunohistochemical positivity for S-100, mammaglobin, and cytokeratin helps distinguish MASC from other salivary gland tumors [7]. Moreover, like secretory breast carcinoma, MASC harbors a recurrent balanced chromosomal translocation, t(12;15)(p13;q25), which leads to the fusion of the *ETV6* gene on chromosome 12 with the *NTRK3* gene on chromosome 15 [8].

Because of the relative rarity of the disease and the lack of follow-up information about it, clinicians have difficulty assessing the prognosis and treatment response of MASC. In view of the lack of detailed information about the clinical characteristics of this tumor, we report here for the first time a case of MASC in the parotid of



**Figure 1.** MRI of a 36-year-old man with MASC. (A) Non-enhanced T1-weighted sequences demonstrate an incompletely encapsulated mass in the right parotid gland. The mass is hypointense relative to the parotid gland. (B) T2-weighted fat-saturated sequences show a mass with mild hyperintensity relative to the parotid gland. (C) and (D) Axial (C) and coronal (D) contrast-enhanced T1-weighted sequences demonstrate a mass with heterogeneous enhancement, a ring-like enhancing margin, and no obvious necrosis.

an adult male patient. This report provides novel information about the clinical features and management of MASC and may inform new strategies for selecting treatments most likely to improve survival and provide a better quality of life for MASC patients.

### Case

A 36-year-old man without significant previous medical or family history had a 3-year history of a slowly growing painless mass in his right parotid. Physical examination revealed a smooth, relatively fixed 3.0 cm × 2.5 cm oval neoplasm without well-defined borders under the right earlobe. The patient reported having no tenderness in the area, had normal facial nerve function, and could close both eyes, bulge both cheeks, and whistle normally.

Magnetic resonance imaging (MRI) showed an incompletely circumscribed, 3.2 cm × 2.6 cm heterogeneously enhancing polycystic mass in

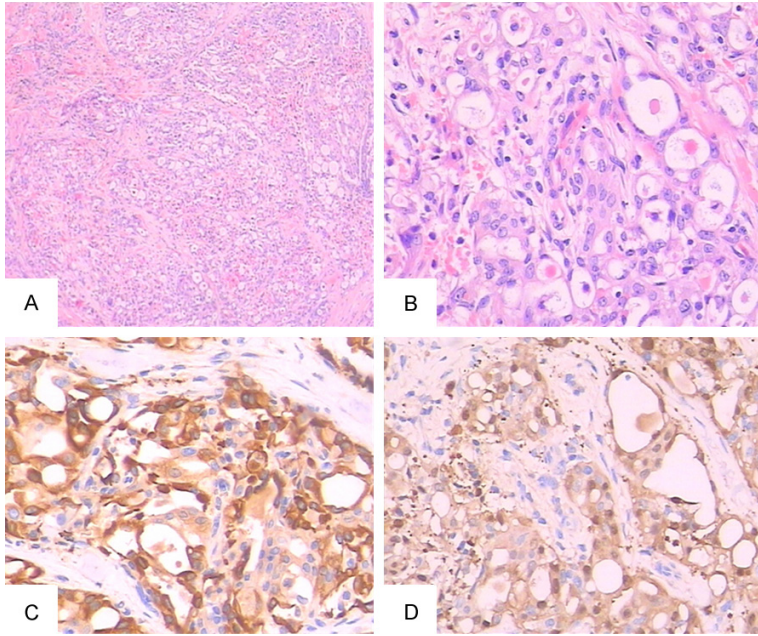
the right parotid gland. The mass was incompletely encapsulated; on non-enhanced T1-weighted sequences, the mass showed hypointensity relative to muscle, and on T2-weighted sequences, the mass showed mild hyperintensity relative to the parotid gland. Both axial and coronal contrast-enhanced T1-weighted sequences demonstrated a mass of heterogeneous enhancement with a ring-like enhancing margin and no obvious necrosis (**Figure 1**).

Based on the findings described above, a provisional diagnosis of suspected low-grade malignancy of the parotid was made, and the patient underwent a parotidectomy with facial nerve preservation. Intraoperatively, the mass was discovered to be located in the deep lobe of the parotid, extending to the mastoid process. The mass was unencapsulated and was removed with caution and proper protection of the facial nerve. The resected mass was 2.5 cm × 2.0 cm × 1.5 cm; bisection of the mass revealed its interior to have the appearance of a soft, solid, gray-red lobulated nodule.

Based on the absence of pathologic nodes in the lower part of the parotid and the findings of rapid intraoperative frozen section, a diagnosis of pleomorphic adenoma was recommended. However, previous experience indicated that a diagnosis of malignancy should be strongly considered for parotid masses with ill-defined borders on imaging and incomplete capsules. Therefore, an extending parotidectomy with nerve preservation and locoregional lymph node dissection was performed.

Based on the final pathology results for the large parotid tumor, a diagnosis of MASC of the salivary gland was recommended. Vascular tumor emboli and nerve bundle membrane invasion were not found, and the local lymph node showed reactive lymphoid hyperplasia.

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**Figure 2.** Immunohistochemical staining. (A) MASC shows a lobulated growth pattern with microcystic/solid and tubular structures that is divided by fibrous septa. (B) MASC has uniform cells with bland-looking vesicular nuclei and abundant homogeneous or bubbly eosinophilic secretory material. (C) and (D) MASC shows (C) diffuse, strong S-100 protein expression and (D) strong mammaglobin expression.

On immunohistochemical analysis, staining for S-100, mammaglobin, vimentin, and GCDFP15 was positive, and staining for CerbB2 and P63 was negative (**Figure 2**). Based on the histological assessment, a tumor stage of T2N0M0 was assigned.

The patient's case was discussed by a multidisciplinary tumor board, which made a final recommendation for postoperative radiotherapy. The patient thus underwent 30 cycles of regional radiotherapy to a total dose of 60 Gy.

One month after completing treatment, the patient had obvious unilateral facial nerve paralysis and could not bulge his cheeks or whistle normally. However, 3 months after treatment, he had recovered much of his facial nerve function and had only a minor distortion of commissure. Eighteen months after treatment, the patient had no sign of nerve malfunction and no evidence of disease recurrence.

### Discussion

Since Skalova et al. first reported 16 MASC cases in 2010, more than 100 such cases have been reported [9]. Most of these reports have described the genetic and histologic aspects of

the tumor, whereas the current case report focuses on the clinical characteristics of MASC. To the best of our knowledge, ours is the first case report of MASC to describe the clinical management of the disease in China.

### Differential diagnosis

Previously, MASC was most commonly diagnosed as acinic cell carcinoma, mucoepidermoid carcinoma, or cystadenocarcinoma or as adenocarcinoma not otherwise specified [1, 2, 4, 6, 7, 10, 11]. Salivary gland tumors that exhibit the classic histologic characteristics of MASC and strong positive staining for mammaglobin and S-100 require a diagnosis of MASC [2, 7]. In the present case, histologic analysis confirmed low-grade MASC. Morphologically, the tumor showed

a microcystic growth pattern, with eosinophilic secretions scattered in the lumina, along with uniform nuclei. Acinic cell carcinoma was ruled out because the distinct blue-purple zymogen granules that characterize that disease were absent [6]. Immunohistochemical results indicated strong positive staining for mammaglobin and S-100; however, these markers should be used together with morphology, since many other salivary gland tumors, such as monomorphic and pleomorphic adenomas, polymorphous low-grade adenocarcinomas, and adenoid cystic carcinomas, can also show positive staining for these markers [12]. Testing for the *ETV6-NTRK3* gene fusion is normally used for the definitive diagnosis of MASC [1, 13], but such highly specialized testing is not feasible for most laboratories. Therefore, other diagnostic criteria for MASC, e.g., a salivary gland tumor with the classic histology of MASC and strong staining for mammaglobin and S-100, should be also considered.

### Role of fine-needle aspiration and intraoperative frozen section analysis

The histological features of MASC and those of low-grade salivary malignancies overlap con-

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siderably. Many clinicians and pathologists use fine-needle aspiration (FNA) of salivary gland lesions because it is a technically simple procedure. Analyzing FNA specimens may help in identifying such lesions. However, one study showed that only 1 of 12 cases of MASC was initially correctly diagnosed as MASC based on FNA cytology [11].

Frozen section analysis is a diagnostic modality that is essential to determining intraoperative management. It is also helpful in assessing margins of resection and/or tumor involvement of nerves and/or vessels [14]. In the present case, because surgery revealed the mass to have an incomplete capsule and to adjoin the trunk of the facial nerve, intraoperative frozen section analysis was needed to verify the provisional diagnosis low-grade malignancy. However, the frozen section results were inconsistent with those for a low-grade malignancy. On the basis of these results, the preoperative imaging studies, and the intraoperative findings, we performed a total parotidectomy with nerve preservation and locoregional lymph node dissection.

The present case, along with other published cases of MASC, demonstrates the limitations of FNA and frozen section analysis in diagnosing MASC. Thus, the upfront diagnosis of MASC requires considerable awareness about the disease and a high index of suspicion for the malignancy. Additional data about the use of both FNA and frozen section analysis in combination with clinical experience is needed to improve the accurate diagnosis of MASC. In the meantime, physicians should use their clinical experience to diagnose this newly recognized neoplasm.

### *Imaging*

The most common ancillary examination used for the diagnosis of a parotid mass is MRI. On MRI, MASC often appears as a well-circumscribed lesion that exhibits a hyperintensity relative to muscle on T1-weighted sequences and a hypointensity relative to the parotid gland on T2-weighted sequences [4]. The MASC in the present case also had this appearance on MRI, except that it was incompletely circumscribed. The incomplete encapsulation of a parotid mass on MRI indicates that a low-grade malignant tumor cannot be excluded. In the present

case, a diagnosis of pleomorphic adenoma was made based on intraoperative frozen section findings, which contradicts this recommendation. Nevertheless, disparate preoperative MRI and intraoperative frozen section findings, such as those seen in the present case and others, should prompt the consideration of extended parotidectomy and locoregional lymph node dissection.

### *Treatment and prognosis*

The most common clinical manifestation of MASC is a slowly growing, painless nodule that is not easily detected. Patients with these tumors rarely present with facial nerve dysfunction; in one review, only 1 of 59 MASC patients had facial paralysis [11]. In the present case, surgery revealed an unencapsulated mass, which was removed with caution and protection of the facial nerve. For MASC patients without preoperative facial paralysis, the final pathologic results show no nerve bundle membrane invasion, and any postoperative facial paralysis can be attributed to the tractive injury of the surgery.

The treatment for MASC varies from simple excisions to radical resections with or without neck dissections, adjuvant radiotherapy, and/or adjuvant systemic chemotherapy [1, 11, 15]. The standard care for low-grade malignant salivary gland tumors is radical surgical resection. Postoperative radiotherapy is reserved for patients with close surgical margins (< 5 mm), incomplete resection, perineural invasion, and/or T3 or T4 tumors [16, 17]. Generally, like acinic cell carcinoma, MASC behaves like a low-grade malignancy but may have a slight propensity for local recurrence, lymph nodes metastasis, lymphovascular invasion, and perineural invasion [18]. The best treatment for patients with these tumors is unclear, but published data indicate that adjuvant therapy offers some benefit. Thus, although the present case was confirmed to be stage T2N0M0 MASC, the multidisciplinary tumor board still recommended that the patient receive postoperative radiotherapy.

Generally, information about the prognosis of MASC is very limited because cases are sporadic and lack systematic follow-up. Chiosa et al., using death or recurrence as the endpoint, reported a mean disease-free survival time of

92 months [15]. Jung et al. [19] followed 9 patients, of whom 3 had local recurrence a median of 44 months (range, 10-101 months) after diagnosis and 2 had lymph node metastases 62 months and 70 months, respectively, after diagnosis. To date, only 4 patients have been reported to die from the disease [1, 15]. In the present case, the patient had no signs of nerve malfunction and no evidence of disease recurrence 1 year after treatment.

### Conclusions

The tumor in the present case exhibited some of the classic histologic characteristics of MASC-e.g., strong immunohistochemical staining for mammaglobin and S-100-and met the criteria for a diagnosis of MASC. Currently, differentiating between MASC and benign or low-grade salivary gland tumors on the basis of these tumors' clinical characteristics is difficult. Improving the means with which to diagnose and treat MASC requires detailed analyses for detecting correlations between the clinical and surgical characteristics of the disease and the recommendations of multidisciplinary tumor boards. In the meantime, a diagnosis of MASC should be strongly considered for any tumors arising from the salivary glands. Additional research of the clinical behavior and prognosis of MASC is needed to generate guidelines for the appropriate treatment of this tumor.

### Acknowledgements

The authors thank Dr. Donglan Luo and Dr. Lingyi Fu, Department of Pathology of Guangdong general hospital, for consultation on the histopathological diagnosis of this case.

### Disclosure of conflict of interest

None.

### Abbreviations

MASC, Mammary analogue secretory carcinoma; ACiCC, acinic cell carcinoma; MRI, magnetic resonance imaging; FNA, fine needle aspiration; FS, frozen section.

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