Int. J. Oral Maxillofac. Surg. 2019; 48: 865–868
https://doi.org/10.1016/j.ijom.2019.01.027, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Case Report
Head and Neck Oncology

Locally advanced mammary analogue secretory carcinoma of the parotid gland

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N. Tokuzen, H. Goda, K. Nakashiro: Locally advanced mammary analogue secretory carcinoma of the parotid gland. Int. J. Oral Maxillofac. Surg. 2019; 48: 865–868.

Abstract. Mammary analogue secretory carcinoma (MASC) has recently been recognized as a salivary gland tumour that is characterized by the ETV6–NTRK3 fusion gene. A case of locally advanced MASC of the parotid gland in a 67-year-old man is presented here. The patient visited the hospital due to a large right infra-auricular mass, which had been enlarging gradually over a period of 2 years. Contrast-enhanced computed tomography (CT) demonstrated a multilocular mass, 75 × 63 mm in size, containing a fluid component with non-uniform contrast effects in the interior portion. The mass had invaded the orbit, skull base, and parapharyngeal space. The patient had neither lymph node nor distant metastasis. The tumour showed tubular and ductal proliferation lined by a single layer of neoplastic cuboidal cells with clear foamy cytoplasm. Characteristic hobnail cells were observed. Expression of ETV6–NTRK3 fusion transcript in the tumour tissues was confirmed by RT-PCR. The final diagnosis was MASC (T4bN0M0, stage IVB). The patient received cetuximab together with radiotherapy at a total dose of 66 Gy. After treatment, CT showed a slightly reduced tumour volume, indicating stable disease. More than 56 months after treatment, the patient remains alive with no remarkable change in the tumour.

Key words: mammary analogue secretory carcinoma; parotid gland; ETV6–NTRK3 fusion gene; bioradiotherapy.

Accepted for publication 26 January 2019
Available online 15 February 2019

Mammary analogue secretory carcinoma (MASC) has recently been recognized as a pathological entity arising in the salivary glands. A case series study of 16 patients with this salivary gland tumour reported that the tumours showed histological and molecular features that were identical to breast secretory carcinoma[1]. MASC harbours a distinct immunohistochemical profile and the specific cytogenetic translocation (12;15)(q13;q25), resulting in an ETS variant gene 6 (ETV6)–neurotrophic tyrosine receptor kinase type 3 (NTRK3) fusion gene[1]. This fusion gene encodes a chimeric tyrosine kinase that has potential transformation activity and plays a major role in carcinogenesis[2]. Histopathologically, MASC is a distinctive entity, and histology in combination with appropriate immunohistochemical examination is sufficient for a diagnosis in most cases. However, several histopathological features of MASC overlap with those of other salivary gland tumours, such as acinic cell carcinoma (AciCC), adenocarcinoma not otherwise specified (ADC-NOS), and low-grade mucoepidermoid carcinoma[1–3]. Similar to other low-grade malignant salivary gland tumours, MASC has been treated primarily with surgical resection.

0901-5027/070865 + 04

Case report

A 67-year-old man attended Ehime University Hospital due to a large right infra-auricular mass, which had been enlarging gradually over a period of 2 years (**Supplementary Material**, Fig. S1). A contrast-enhanced computed tomography (CT) scan demonstrated a multilocular mass, 75 × 63 mm in size, containing a fluid component with non-uniform contrast effects in the interior portion. The mass had invaded the orbit, skull base, and parapharyngeal space (Fig. 1). There was no evidence of either regional lymph node metastasis or distant metastasis. The provisional diagnosis was malignant parotid tumour, cT4bN0M0, stage IVB.

The patient underwent biopsy under general anaesthesia. The biopsy revealed a tubular and ductal neoplastic glandular proliferation characterized by a single layer of cuboidal cells with eosinophilic cytoplasm. The tumour cells contained a round or oval nucleus and one or two distinctive nucleoli. Characteristic hobnail cells were observed protruding into the glandular lumens. The mitotic index was low. The tumour parenchyma was surrounded by eosinophilic hyaline stroma and abundant microvasculature. Diastase–Periodic acid–Schiff (d-PAS) staining-positive fine secretory granules were seen in the cytoplasm (Fig. 2). The tubular lumen contained colloidal fluid, which was positive for antitrypsin, lactoferrin, and immunoglobulin A (IgA). The tumour cells were positive for vimentin, S-100, mammaglobin, and epidermal growth factor receptor (EGFR) proteins (Fig. 2), and negative for oestrogen receptor (ER) and α-smooth muscle actin (SMA).

The presence of ETV6–NTRK3 fusion transcript in the tumour tissues was subsequently confirmed by reverse transcription (RT)-PCR and direct DNA sequencing (**Supplementary Material**, Fig. S2). Based on these findings, a final diagnosis of locally advanced unresectable MASC was made.

The overexpression of EGFR in the tumour cells prompted us to start treatment with radiotherapy at a total dose of 66 Gy, together with cetuximab (400 mg/m^2 the first week and 250 mg/m^2 for the next 7weeks). A CT scan performed 1 month after completion of the bioradiotherapy showed a slightly reduced tumour volume, indicating stable disease. More than 56 months after treatment, the patient remains alive and has maintained quality of life, with no remarkable change in the tumour.

Discussion

MASC has been described as a low-grade malignant salivary gland tumour composed of carcinoma cells with pink vacuolated cytoplasm forming microcystic, tubular, or solid patterns, and uniformly expressing mammaglobin and S-100 proteins. The study by Skálová et al.[1] indicated ETV6 gene rearrangement by fluorescence in situ hybridization (FISH) and ETV6–NTRK3 fusion by RT-PCR. This fusion protein leads to the constitutive activation of two major effector pathways, the Ras–mitogen-activated protein (MAP) kinase mitogenic pathway and the phosphatidyl inositol-3-kinase (PI3 K)-AKT pathway[3].

Since the first description of MASC, more than 230 cases of MASC have been described in case series and case reports[4–7]. Immunostaining of mammaglobin and S-100 protein is useful for the diagnosis of MASC, but the detection of ETV6–NTRK3 fusion gene expression seems to be essential. Similar to other low-grade malignant salivary gland tumours, MASC has been treated primarily with surgical resection, and several patients have received postoperative radiotherapy. The clinical course is favourable with a low rate of recurrence and excellent overall and disease-free survival[8]. Therefore, few cases have been treated with chemoradiotherapy alone. Although there has been a reported case of high-grade MASC with loss of CDKN2A/B treated with crizotinib, the efficacy of this drug was found to be limited[9]. In the case presented here, EGFR was overexpressed in the tumour cells, and treatment comprising radiotherapy with cetuximab was used. After this bioradiotherapy, the tumour volume

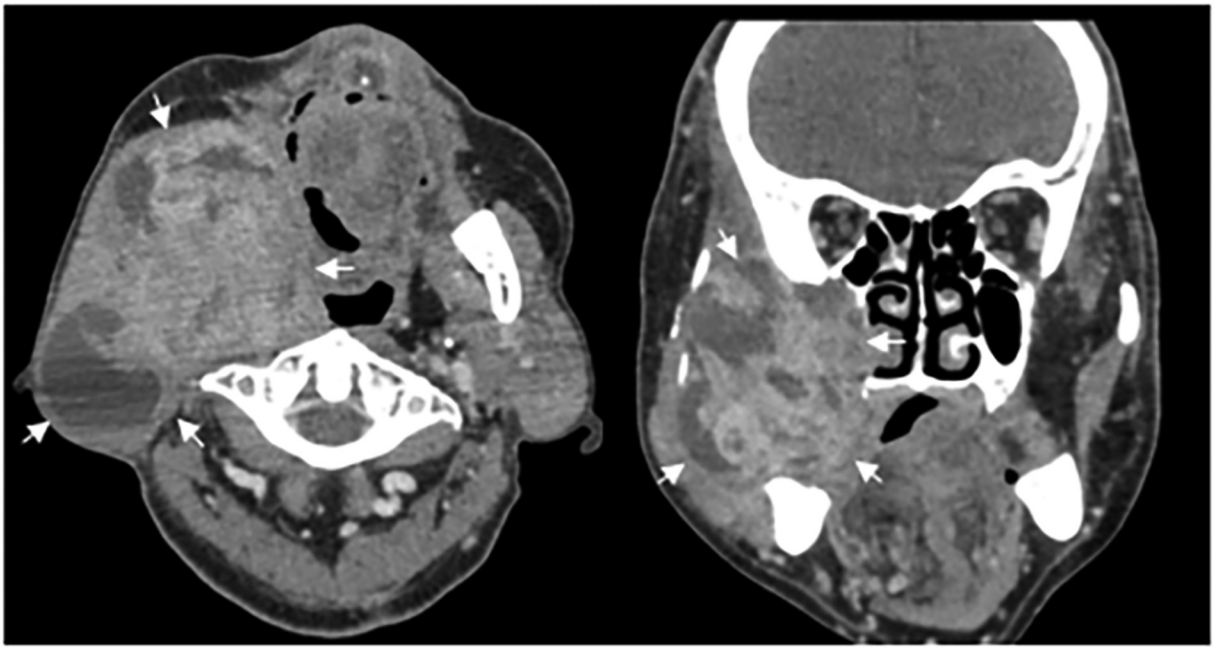

Fig. 1. Contrast-enhanced CT images of the tumour. A tumour of 75 × 63 mm in size was present in the right parotid gland. The tumour was relatively well circumscribed and contained a low-density area. The arrows indicate the extent of the tumour.

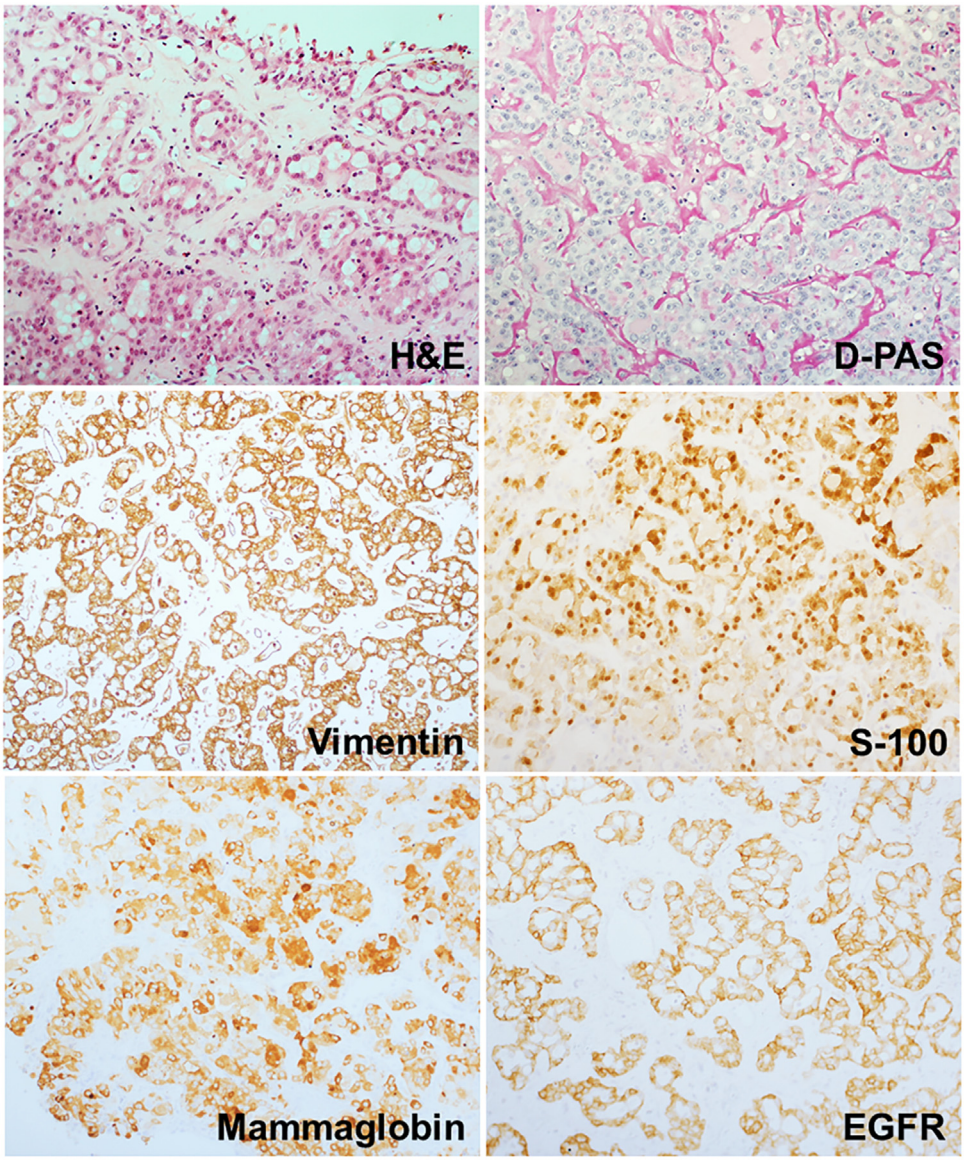

Fig. 2. Histopathology of the tumour. The tumour consisted of a proliferation of tubular and ductal glandular epithelium lined by a single layer of cuboidal cells with eosinophilic cytoplasm (H&E staining, × 40). A few d-PAS positive-staining fine secretory granules were noted in the cytoplasm. On immunohistochemical staining, tumour cells were positive for vimentin, S-100, mammaglobin, and EGFR proteins. (H&E, haematoxylin and eosin; d-PAS, diastase–Periodic acid–Schiff; EGFR, epidermal growth factor receptor.).

was slightly reduced, resulting in stable disease.

This report is novel in describing a case of MASC treated with cetuximab plus radiotherapy. However, several recent clinical trials have demonstrated the anti-tumour activity of tropomyosin-related kinase (TRK) inhibitors in patients with NTRK-rearranged malignancies. Specifically, larotrectinib and entrectinib have been shown to be potent, safe, and promising TRK inhibitors[10]. Targeting NTR proteins appears to be a useful treatment for patients with unresectable MASC.

Funding

None.

Competing interests

None.

Ethical approval

Not required.

Patient consent

Written informed consent was obtained from the patient.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2019.01.027.

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