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Mammary analogue secretory carcinoma (MASC): A literature review and report of two cases

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Abstract

Introduction: Mammary analogue secretory carcinoma (MASC) is a rare salivary gland tumour. It is generally a low-grade lesion that presents as a slow growing painless swelling with an indolent course with good survival. Diagnosis is typically via the highly specific ETV6-NTKR3 gene fusion with the translocation t(12;15)(q13;q25).

Method: A literature review was conducted through PubMed, Cochrane, and Medline. We also present two cases.

Results: Although typically regarded as a low-grade lesion, high-grade features, such as nodal metastases, more solid and trabecular architecture with necrosis, and the ETV6-X fusion gene, have been described. Our cases were diagnosed through morphologic and immunohistochemical features despite absence of the classic fusion gene.

Conclusion: MASC can be diagnosed in absence of the highly specific ETV6-NTKR3 in presence of certain morphologic and immunohistochemical features. Although it is a typically low-grade lesion, several high-grade features have been described that may require further treatment.

Keywords: head and neck neoplasms; salivary gland; parotid gland; salivary gland neoplasms; parotid neoplasms; immunohistochemistry; mammary analogue secretory carcinoma.

Introduction

Mammary Analogue Secretory Carcinoma (MASC) is a rare, relatively recently described salivary gland tumour, with the first being reported by Skalova et al. in 2010 [1]. Since then, some 300 cases have been published in the literature.

Epidemiology

The true incidence is unknown due to rarity and previous misclassification. Luk et al. found 9 MASC cases in a review of 190 malignant salivary gland tumours (4.5%), whereas Majewska et al. found 7 MASC cases in a review of 183 cases (4%) in a similar study [2,3].

Clinical presentation

It most commonly occurs in the parotid gland, but it can also arise from minor salivary glands in the lips, hard palate, base of tongue, as well as submandibular gland [4-6].

It is a low-grade tumour that typically presents as a slow-growing, painless swelling, though high-grade lesions presenting with pain and facial nerve paresis have been reported [4,5,7,8]. It occasionally has extracapsular extension, perineural invasion, and cervical nodal metastasis, whilst distant metastasis is rare [4,9]. Local recurrence is uncommon [5]. Despite it usually behaving indolently, it can also behave more aggressively, howev-

er there are no definitive prognostic factors to help differentiate this currently. Treatment is typically by gland extirpation, with or without neck dissection, and sometimes radiation therapy. However, given the rarity and lack of prognosticating factors, there are no consensus regarding treatment and follow up [4].

Histopathology

In WHO 2017 4th Edition Classification of Salivary Tumours, in addition to introducing the concept of high-grade transformation and modification of salivary carcinomas including polymorphous and cribriform adenocarcinoma, clear cell carcinoma, intraductal carcinoma, there are three new entities that have been added including MASC, sclerosing polycystic adenosis and intercalated duct lesions [10].

MASC shares the morphology and genetics of secretory carcinoma of the breast, a subtype of infiltrating ductal carcinoma, which is equally rare [1]. Previously it has been labelled as acinic cell carcinoma, mucoepidermoid carcinoma, and adenocarcinoma, not otherwise specified [11,12]. It typically occurs in young male patients, with a mean age of 46 years old [4]. However, paediatric cases have been reported [13,14]. The defining characteristic is the ETV6-NTRK3 fusion and translocation: t(12;15) (q13;q25), which can both be identified on FISH or PCR [1]. This translocation has also been identified in infantile fibrosarcoma and congenital mesoblastic nephroma [15]. Cases without classical ETV6 gene rearrangement may harbour alternative gene rearrangements ("ETV6-X fusion") that may be associated with more aggressive clinical course of the disease [16].

Grossly it is a well-circumscribed, unencapsulated multilobulated mass, subdivided into smaller segments by fibrous septa. Microscopically the tumour cells have uniform round and vesicular nuclei with central nucleoli and eosinophilic pink vacuolated cytoplasm. Cells are arranged into microcystic, cribriform, tubular, papillary, follicular or solid nests. Microscopic foci of invasion are often present, but the overall mitotic activity is low. High grade MASC variations are characterised by a more solid and trabecular architecture with necrosis, diminished secretions, larger cells and more prominent nucleoli with atypia [6].

Intraluminal secretions may be seen in the microcystic or tubular structures. Such material is usually mucicarmine, periodic acid-Schiff (PAS), and Alcian blue positive. It also stains with antibodies to epithelial membrane antigen (EMA). The microscopic features of MASC can be also recognized cytologically by fine-needle aspiration biopsy. Cells are positive for a wide-spectrum of cytokeratins (e.g. AE1/AE3, Cam5.2), low-molecular weight cytokeratins (CK7, CK8, CK19), vimentin, S-100, mammaglobin, GCDFP-15, MUC1, GATA-binding protein 3, adipophilin, α -amylase, DOG-1, SOX-10, and p63 [6].

Here we present two cases of MASC involving the parotid gland that were managed in our centre.

Case I

A 35-year-old man presented with one year of painless firm and mobile left parotid lump of about 2 cm which has not changed in size. There were no cranial nerve deficits on exam. He had a background of obesity, gout, asthma, depression, non-smoker, and previous excess alcohol and methamphetamine intake. He is of New Zealand Maori background.

An MRI showed a superficial lobe tumour, with no pathological neck nodes (Figure 1). Subsequent core biopsy suggested a secretory carcinoma although it was ETV6 negative on FISH. The patient proceeded to superficial parotidectomy with preservation of facial nerve and without neck dissection (Figure 2).

The surgical specimen showed a 25 X 15 X 15 mm well-circumscribed but unencapsulated lesion with soft creamy yellow areas and firmer pale areas. The lesion was completely excised with closest margin of 3 mm and no involved lymph nodes or perineural invasion. Microscopically the tumour had lobules of cells with solid and microcystic growth pattern, with lobules separated by fibrous septa. There were also associated infiltrates of plasma cells and lymphocytes. The tumour cells contained small round nuclei with occasional mitoses (mitotic rate 1 in 10 high power fields). No PAS positive zymogen granules were identified.

FISH was repeated but was negative for ETV6 re-arrangement. A diagnosis of MASC was made based on morphology, presence of S100, Mammaglobin, GCDFP15, and negative DOG1 (Table 1). Multidisciplinary consensus favoured clinical observation without post-operative radiotherapy. There was no evidence of recurrence at 12 months following his operation.



Figure 1: MRI of Case 1 with evidence of T1 hypointense and T2 hyperintense well-defined, though lobulated soft tissue density lesion in the superficial lobe of the left parotid. The lesion measures approximately 14 x 14 x 11mm. There is no fat suppression seen on fat-sat sequences. On diffusion weighted there is significant diffusion restriction and loss of signal on ADC sequence.

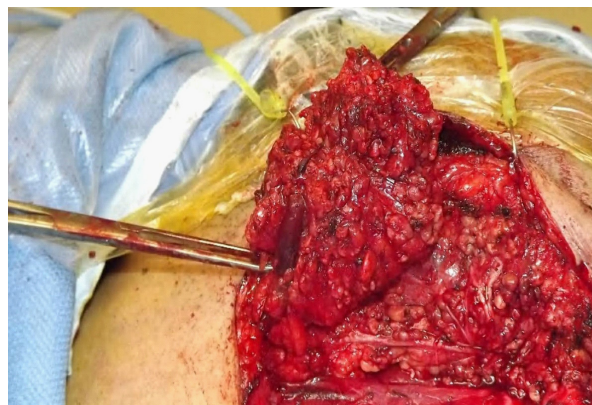


Figure 2: Intraoperative photo of Case 1 demonstrating removal of lesion via superficial parotidectomy.

Case II

A 65-year-old man presented with one year of painless 3 cm firm left parotid lump with limited mobility, reportedly to be gradually enlarging. He is a non-smoker or drinker of alcohol and is otherwise well. He is of New Zealand Maori background.

An MRI and CT showed a large 60 x 38 x 37 mm mass in left parotid, involving the deep lobe, extending into parapharyngeal space with mild compression of the carotid artery, but no lymph node involvement (Figure 3). He proceeded to core biopsy which was suggestive for secretory carcinoma, with FISH negative for ETV6 re-arrangement.

He proceeded to total conservative parotidectomy, parapharyngeal mass excision and selective neck dissection (Figure 4).

Final histology showed a completely excised, encapsulated parotid tumour 80 X 27 X 25 mm with solid and cystic components. Microscopically there are solid, nested, as well as infiltrative cord-like architecture. Cytologically there were cells with eosinophilia as well as focally vacuolated cytoplasm. Nuclei are uniform with occasional small but prominent nucleoli. No mitotic activity was seen. There was no perineural invasion and no involved lymph nodes. Immunohistochemical results are shown in Table 1.

Table 1: Immunohistochemistry (IHC) features of cases.

IHC	Case 1	Case 2
S100	+	+
Mammoglobin	+	+
CK5/6	-	+
SOX10	-	+
GCDFP15	+	-
DOG1	-	-
BOB1	-	-
Mel A	-	-
P40	-	-
MUC1	+	-
CK8/18	+	+
CK19	+	+
Vimentin	+	+
SMA	-	-
GATA3	-	-
CK7	+	+

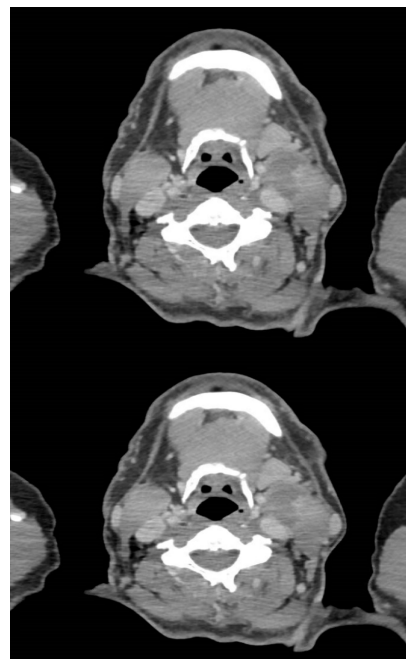


Figure 3: Case 2 with A) MRI with a mildly T1 hyperintense, moderately T2 hyperintense 60 X 38 X 37mm enhancing solid with cystic component lobulated mass centred within the deep lob of the left parotid gland with extension anteroinferiorly into the left submandibular gland, displacing the retromandibular vein and the superficial temporal artery. There is also mild extrinsic compression on the carotid. No lymphadenopathy. B) CT: A 76 X 35 X 28mm dumb-bell shaped mass in the left parotid gland. It displaces the adjacent structures, including the jugular vein and carotid artery, but not evidently invading it.

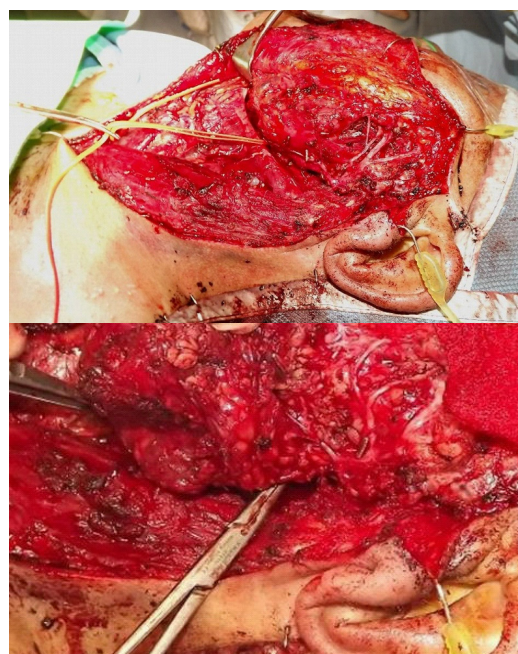


Figure 5: Intraoperative photo of Case 2 demonstrating removal of lesion through the deep lobe of the parotid gland.

Discussion

These cases demonstrate a typical presentation of MASC with a painless parotid swelling. The original core biopsies were suggestive of MASC, despite both not having the classic ETV6 rearrangement, which is specific to MASC in salivary cancers. As described in literature, a diagnosis of MASC can be made without the classic ETV6 fusion gene providing there is sufficient cytologic and immunohistochemical features [17] (Table 2).

These features are lobulated growth pattern, homogenous eosinophilic secretions, no PAS positive secretory zymogen granules, expression of S-100, mammoglobin, and vimetin [17,18]. Nevertheless, one must be mindful that mammoglobin reactivity can be found in a small proportion of low-grade cribriform cystadenoma, polymorphous low-grade adenocarcinoma, mucoepidermoid carcinomas, and pleomorphic adenomas, hence they are differentials in diagnosis of MASC [19]. Furthermore, co-reactivity of mammoglobin and S-100 were found in polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma [20,21]. As such, the diagnosis of MASC should not be made based on mammoglobin and S-100 reactivity alone, despite their high sensitivity.

An important differential diagnosis, both in terms of indolent behaviour and similar histological features is acinic cell carcinoma. It has been reported by Bishop et al. that a significant number of salivary acinic cell carcinomas have been reclassified as MASC [11]. The key difference is that acinic cell does not have the ETV6 gene rearrangement. It also typically has basophilic

staining cytoplasm with PAS-positive zymogen granules instead of eosinophilic staining [4,6]. However, zymogen-poor acinic cell carcinomas do exist, though it is many of these that have been reclassified into MASC on subsequent review [11].

Although the pathological features of MASC have been well described, management is still controversial given lack of follow up data. Case 2 had a larger, more extensive lesion, however both did not have lymph node metastasis, and both had parotidectomies with preservation of facial nerve, without adjuvant radiotherapy. The mean disease-free survival has been reported to be 92 months, which was not statistically different to acinic cell carcinoma of 121 months [22]. As such, the management could be the similar, with surgical excision without radiotherapy in absence of clinical cervical nodal metastases. In presence of high-grade changes, namely nodal metastases which can occur in up to 25% of cases, more solid and trabecular architecture with necrosis, diminished secretions, larger cells and more prominent nucleoli with atypia, and ETV6-X fusion gene, then neck dissection and/or post-operative radiotherapy could be considered [8,20].

As a fore mentioned, FISH was negative for the classic ETV6 gene rearrangement in our cases, which could mean an alternative gene rearrangement may exist. Such a gene may be associated with more aggressive disease behaviour as described by Bissinger et al, however further studies with larger cohorts are needed to validate this association [16,23]. Both our cases had low-grade features and were thus managed without adjuvant radiotherapy.

Table 2: Typical features of mammary analogue secretory carcinoma (MASC) and its main differentials.

	MASC	AcICC	ANOS	Low-Grade ME
Clinical	Mainly parotid M>F	Mainly parotid F>M 30% symptomatic More likely bilateral	Mainly minor salivary, followed by parotid M>F	50% major salivary 40% symptomatic
Morphologic/ Cytologic	Microcysts, papillary proliferation, cribriform pattern. Vacuolated eosinophilic cytoplasm, "bubbly" appearance. Mucin intracytoplasmic and intraluminal. Does not usually infiltrate surrounding tissue	Solid, microcystic, papillary-cystic, follicular. Serous acinar cells. Variable cell types and architectures. Usually mucin - Basophilic cytoplasm	Infiltrative. Glandular or ductal. Also solid, tubular, nests, islands, cord-like. Collagenised, myxoid, mucinous stroma	Cystic pattern Squamoid/epidermoid, mucinous, intermediate cells
IHC	Strongly positive for Mammoglobin & S-100 STAT5 + GCDP-15 + DOG1 - No zymogen granules p63 -	PAS positive zymogen granules Non-reactive to amylase antibody. STAT5 + DOG 1 + S-100 +	Mucin	Diffuse p63 in squamoid cells S100 - Mammoglobin -
Cytogenetic	ETV6-NTRK3	Nil	Nil	CRTC1 (MECT1)-MAML2

AcICC: acinic cell carcinoma, ANOS: adenocarcinoma, not otherwise specified, ME: mucoepidermoid carcinoma.

Conclusion

It has been ten years since MASC was first described by Skalova. Our understanding of its pathological features has improved, with ETV6 being diagnostic, but acknowledging the utility of various morphologic and immunohistochemical features that would be supportive of MASC in absence of ETV6 gene rearrangement, which helped identify our two cases. Although the clinical presentation has largely remained consistent with the initial description of a low-grade lesion, its management is still uncertain. More studies are needed to elucidate prognostic features. Given the good survival reported to date, it would seem reasonable to manage as other low-grade salivary gland cancers.

Declarations

Acknowledgement: Dr Cynric Temple-Camp for assistance with pathology.

Ethical considerations: This case report follows local research guidelines and does not require IRB approval. Patient information has been anonymised. Clinical photographs and imaging for inclusion in publication has been utilised with consent by patients (signed consents available upon request).

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Key points

1. MASC is a recently described rare, low-grade, salivary gland cancer.
2. Diagnosis can be made without the classic ETV6-NTRK3 fusion gene.
3. Co-reactivity of Mammaglobin and S-100 is sensitive but not specific for MASC.
4. Potential high-grade features, including ETV6-X fusion gene, exist, but further studies are needed to validate this association.
5. Management is typically via extirpation of lesion with or without neck dissection and adjuvant radiation therapy.

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