Case Report

Secretory carcinoma of the parotid: Approach with morphology, cyto-immunohistochemistry, and fluorescence *in situ* hybridization analysis of the rare entity

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ABSTRACT

Mammary analog secretory carcinoma (MASC) is a recently described entity listed in the World Health Organization classification of the salivary gland tumors under the head and neck tumors. It is a low-grade malignancy with a relatively benign course. The identification of this new but less recognized entity is warranted due to a limited understanding of the prevalence, clinical course, behavior, and prognosis. Here, we present a case of MASC arising in the right parotid gland in a 50-year-old gentleman. It was slow-growing swelling associated with the recent onset of pain. On examination, 4×3 cm swelling was present just below the right ear lobule. It was firm, irregular in shape with a smooth surface with slight mobility to the overlying skin. Fine-needle aspiration cytology suggested differentials of salivary duct carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, and metastatic carcinoma. The patient underwent right superficial parotidectomy with supraomohyoid neck dissection, and histopathology came out to be secretory analog mammary carcinoma. Immunohistochemistry is a confirmatory test that shows positivity for S-100 protein and mammaglobin and shows characteristic *ETV6-NTRK3* translocation.

Key words: Immunohistochemistry, Mammary analog secretory carcinoma, Parotid gland

Recently described, mammary analog secretory carcinoma (MASC) is a rare salivary gland tumor that relates the morphology and genetics of an equally rare malignancy of the breast, the secretory carcinoma. It was first described in the year 2010 by Skalova *et al*. [1]. Both MASC and secretory carcinoma of the breast are immunoreactive for S100, mammaglobin, epithelial membrane antigen, and vimentin and are triple-negative (non-immunoreactive for estrogen receptor, progesterone receptor, and HER2/Neu) [1-3]. It is commonly mistaken for other salivary gland tumors. Identification of MASC is important due to its low-grade histology, non-specific histological findings, and indolent clinical behavior from rather other aggressive salivary tumors such as adenocarcinoma not otherwise specified, acinic cell carcinoma, and mucoepidermoid carcinoma.

Here, we are reporting a case of MASC with a rather adverse clinical course than usually recognized indolent behavior. At present, there are no specific treatment guidelines, and it is treated like any other malignant salivary gland tumor. Further studies are needed to identify the incidence of adverse prognostic factors, along with treatment protocols and clinical behavior on a long-term basis in MASC with high-grade transformation.

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CASE REPORT

A 50-year-old gentleman presented to the otorhinolaryngology department of a local hospital in Bengaluru, India, with complaints of swelling over the right side of the neck. He is a known smoker for the past 15 years (30 pack-years). There was no history of drug allergies or trauma. The swelling had been present from the past 6 months and was gradually increasing in size. It was also associated with a recent onset of pain from the past 2 weeks of moderate-intensity and was localized.

On examination, vitals were within normal limits. The swelling was nodular, firm, irregular, and ill-defined with a smooth surface with limited mobility to the skin and underlying soft tissue. The swelling measured about 4×3 cm with no local rise of temperature. No palpable lymph nodes were identified in the anterior triangle of the neck.

Fine-needle aspiration was done from the swelling and reported with differential diagnoses of salivary duct carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, and metastatic

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carcinoma. Magnetic resonance imaging showed a partly circumscribed solid and cystic mass measuring about 5×3 cm in the right parotid gland. In view of presumed malignant findings, the right superficial parotidectomy with supraomohyoid selective neck dissection was performed.

The right superficial parotidectomy specimen measured about 7×5×3 cm with supraomohyoid neck dissection measuring 8×4×3 cm. The tumor was brown, partly well-circumscribed, and encapsulated measuring 5×3×2.2 cm. Both solid and cystic components containing brownish material were seen (Fig. 1). The external inked margins were free from the lesion. Histologically the tumor showed cystic, solid, tubular, and papillary architecture. The cells displayed low-grade bland morphology with eosinophilic vacuolated bubbly cytoplasm (Fig. 2). Intraluminal and intracellular colloid, such as periodic acid–Schiff (PAS) positive and diastase resistant, were present (Fig. 3). Perineural infiltration and extracapsular extension were observed (Fig. 4). Fourteen lymph nodes were isolated from the supraomohyoid neck dissection, of which one showed the presence of tumor deposit (level 1).

Initial diagnoses of salivary duct carcinoma, acinic cell carcinoma, and the oncocytic variant of mucoepidermoid carcinoma were considered. Immunohistochemistry was performed with S100, mammaglobin, DOG1, and p63. A positive expression for S100 and mammaglobin was observed (Fig. 5). DOG1 and p63 immunostains were negative. Hence, a final diagnosis of mammary analog secretory carcinoma was made. The tumor was further confirmed by fluorescence *in situ* hybridization (FISH) analysis to exhibit characteristic t(12;15)(q13;q25) ETV6-NTRK3 translocation (Fig. 6).

Figure 1: Parotidectomy specimen showcasing solid and cystic encapsulated tumor

DISCUSSION

MASC is most often seen involving the parotid gland (70%) followed by a minor salivary gland in the palate, base of the tongue, and lips [4]. The common age group affected belongs to the fourth or fifth decade. It accounts for <0.3% of the salivary gland tumors [5]. Slight male predilection is noted. It typically presents as a painless mass, with an average size ranging from 0.3 to 8.0 cm [6].

Extension to surrounding parenchyma is uncommon, in contrast to our case, where an extension was seen. Histologically, the pattern of tumor cell arrangement is not specific in MASC. However, the findings of intraluminal or intracytoplasmic PAS-positive diastase resistant non-zymogen secretions are in favor of MASC.

Metastasis to lymph nodes, lymphovascular, and perineural invasion can occur but not well documented. In our case, we did find the presence of all three adverse prognostic components. The disease-free survival period is better than the other salivary gland tumors. In the literature search, 17 patients experienced local recurrence including the three cases reported by Skálová *et al*. [1], four patients' experienced distant metastasis, and only six patients died of the disease including two out of the three cases reported by Skálová *et al*.

MASC expresses S100 and mammaglobin immunomarkers. They may also express GATA3, pan-cytokeratin, CK7, CK8, CK18, CK19, epithelial membrane antigen, vimentin, MUC1, MUC4, STAT5a, GCDFP15, and adipophilin. MASC is typically negative for high-molecular-weight keratin and basal cell/myoepithelial markers, such as calponin, SMA, CK5, CK6, CK14, and p63 [7].

Histologically, the most common differential diagnoses are acinic cell carcinoma and adenocarcinoma, not otherwise specified. In a study done by Chiosea *et al*., about 14/37 and 11/89 tumors of adenocarcinoma and acini cell carcinoma were reclassified as MASC, respectively [8]. Acinar cell carcinoma contains PAS-positive diastase resistance cytoplasmic zymogen granules. However, they are usually reactive for amylase, DOG1 antibodies, and negative for mammaglobin. p63 is expressed in mucoepidermoid carcinoma and is negative in MASC and acinic cell carcinoma.

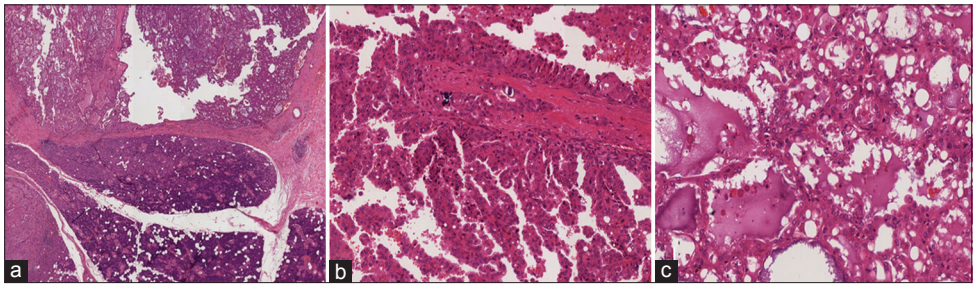

Figure 2: (a) Low power view showing salivary gland with tumor exhibiting solid and cystic change; (b) papillary architecture of tumor; and (c) tubular architecture containing intraluminal and intracellular colloid secretions

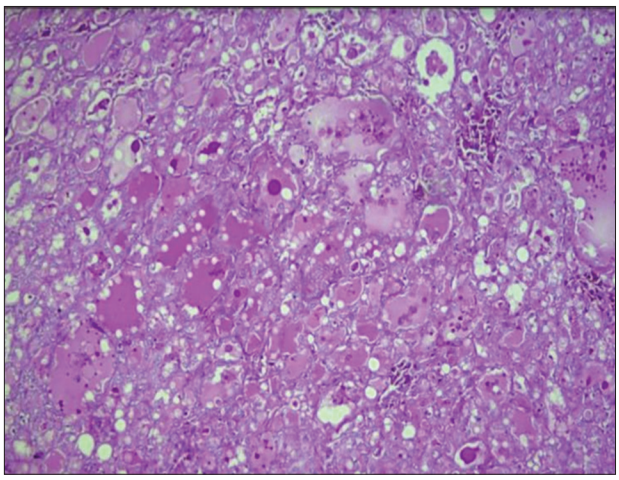

Figure 3: Periodic acid–Schiff positive intraluminal and intracellular colloid material

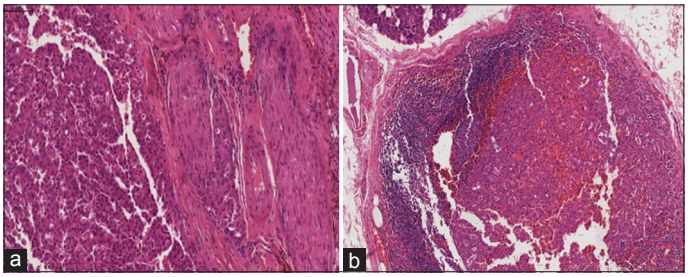

Figure 4: (a) Tumor with perineural infiltration and (b) tumor exhibiting lymph node metastasis

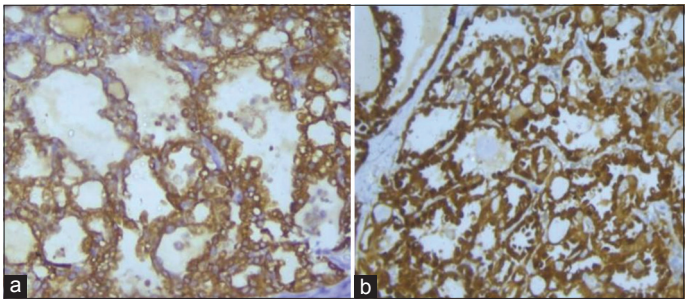

Figure 5: (a) and (b) Immunohistochemistry expression for mammaglobin and S100 by the tumor cells, respectively

Both MASC and breast secretory carcinoma are associated with translocation t(12;15)(p13;q25), which are a fusion of the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15. The fusion gene encodes a chimeric tyrosine kinase, which has potential transformation activity and plays a role in carcinogenesis [9]. We performed a FISH study with an ETV6 break apart probe for molecular genetic analysis and revealed split signals in 60% of the nuclei. This fusion has also been shown in other tumors, including infantile fibrosarcoma, acute myeloid leukemia, and congenital mesoblastic nephroma [10]. Bishop *et al*. reported [11] that approximately 80% of extraparotid acinic cell carcinoma needed to be reclassified as MASC on the basis of an ETV6 translocation together with strong staining for S100 and mammaglobin. Pinto *et al*. reported in their study that 3 out of 6 MASC tumors were initially classified as acinic cell carcinoma [12]. In a study done by Sethi *et al*., 4/91 of the cases

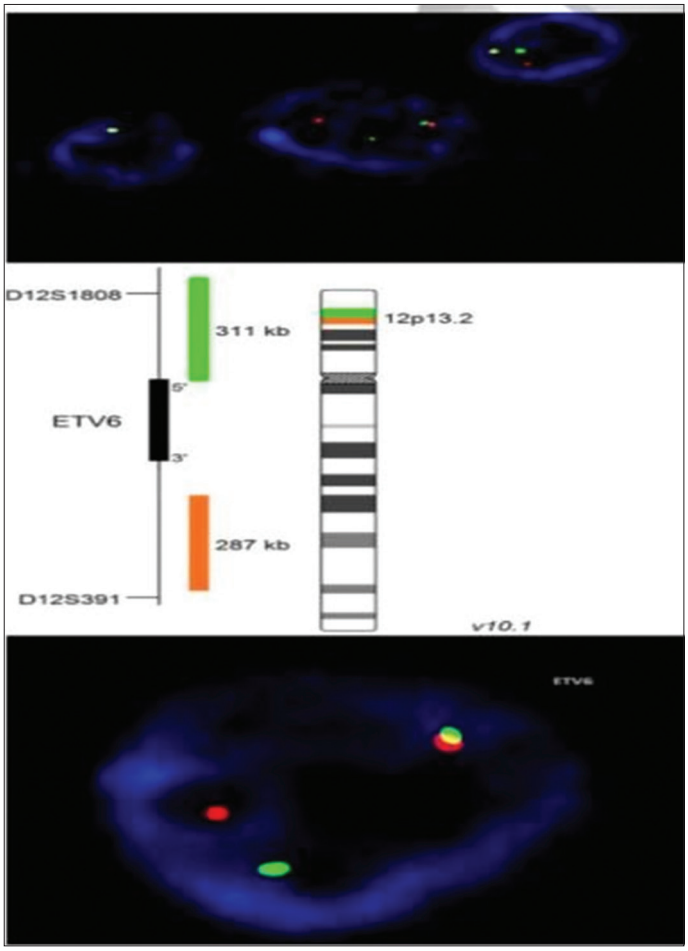

Figure 6: Fluorescence *in situ* hybridization analysis confirming mammary analog secretory carcinoma with characteristic t(12;15)(q13;q25) translocation, a fusion of the ETV6 and NTRK3 gene

studied died of the disease. MASC is usually treated as low-grade malignancy. However, there are cases reported with lymph node metastasis. Few studies have claimed that lymph node metastasis is higher in MASC as compared to acinic cell carcinoma [4].

Treatment varies from localized to extensive surgeries, including neck dissection followed by chemoradiation depending on the prognostication. Our case showed isolated lymph node metastasis in level one group and did not receive chemoradiation. He has been free from disease for 1 year. Targeted therapies in salivary gland tumors are not well investigated and in use. The ETV6-NTRK3 translocation might provide a potential therapeutic target. Further investigations are needed to incorporate targeted therapies for therapeutic options for salivary gland tumors including MASC.

CONCLUSION

MASC has an indolent to the aggressive course. Immunohistochemistry is useful in the diagnosis of MASC in places where cytogenetic analysis is not available.

REFERENCES

1. Skalova A, Vanecek T, Sima R, Laco J, Weinreb I, Perez-Ordonez B, *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;34:599-608.
2. Lae M, Freneaux P, Sastre-Garau X, Chouchane O, Sigal-Zafrani B, Vincent-Salomon A. Secretory breast carcinomas with ETV6-NTRK3 fusion gene belong to the basal-like carcinoma spectrum. Mod Pathol 2009;22:291-8.
3. Tavassoéli FA, Devilee P, editors. Pathology and Genetics Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003.
4. Sethi R, Kozin E, Remenschneider A, Meier J, VanderLaan P, Faquin W, *et al*. Mammary analogue secretory carcinoma: Update on a new diagnosis of salivary gland malignancy. Laryngoscope 2014;124:188-95.
5. Zardawi IM, Hook P. Mammary analogue secretory carcinoma of minor salivary glands. Pathology 2014;46:667-9.
6. Connor A, Perez-Ordonez B, Shago M, Skalova A, Weinreb I. Mammary analog secretory carcinoma of salivary gland origin with the ETV6 gene rearrangement by FISH: Expanded morphologic and immunohistochemical spectrum of a recently described entity. Am J Surg Pathol 2012;36:27-34.
7. Stevens TM, Parekh V. Mammary analogue secretory carcinoma. Arch Pathol Lab Med 2016;140:997-1001.
8. Chiosea SI, Griffith C, Assaad A, Seethala RR. The profile of Acinic cell carcinoma after recognition of mammary analog secretory carcinoma. Am J Surg Pathol 2012;36:343-50.
9. Bishop JA. Unmasking MASC: Bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head Neck Pathol 2013;7:35-9.
10. Bishop JA, Yonescu R, Batista DA, Westra WH, Ali SZ. Cytopathologic features of mammary analogue secretory carcinoma. Cancer Cytopathol 2013;121:228-33.
11. Bishop JA, Yonescu R, Batista DA, Eisele DW, Westra WH. Most non-parotid Acinic cell carcinomas represent mammary analog secretory carcinomas. Am J Surg Pathol 2013;37:1053-7.
12. Pinto A, Nosé V, Rojas C, Fan YS, Gomez-Fernandez C. Searching for mammary analog secretory carcinoma of salivary gland among its mimics. Mod Pathol 2014;27:30-7.

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