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CASE REPORT

Secretory Carcinoma of Parotid and Diagnostic Challenge of Salivary Gland Malignancy

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Secretory carcinoma (SC) or also known as mammary analogue secretory carcinoma (MASC) is a new distinct entity of salivary gland carcinoma that histopathologically resemble secretory carcinoma of breast. It was first documented in salivary gland in 2010 and included in World Health Organization classification in 2017. Formerly it was misdiagnosed as acinic cell carcinoma or adenocarcinoma in majority of cases, but comparably it is more aggressive. Present of translocation mutation t (12;15) (p13; q25) with fusion of ETV6-NTRK3 genes is typical feature for SC that absent in other salivary gland neoplasm. Diagnostic challenges are always seen in salivary gland tumor due to the morphological diversity, rapid change in nomenclature, some subtypes are extremely rare and lack of specific laboratory test in some center. Surgery is the mainstay of treatment same as other salivary gland carcinoma but increasing evidence of alternative medical treatment with tropomyosin receptor kinase antagonist that make SC more special.

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A 39-year-old male, with no underlying medical illness, presented to the Otorhinolaryngology clinic with a history of right infra-auricular swelling for 2 years duration. It was gradually increasing in size. Initially was painless but became painful on mouth opening over the past 2 months. It was associated with trismus and reduced oral intake for 6 months duration. There was no facial weakness, constitutional symptoms, or obstructive symptoms.

On examination, there was 4cm x 4cm swelling at the right angle of the mandible, hard in consistency, irregular surface, non-tender and appeared fixed to the overlying skin and underlying structures. The facial nerve was intact and no cervical lymph node was palpable. There was presence of trismus, but no medialization of the lateral oropharyngeal wall. Flexible nasopharyngolaryngoscopy revealed normal findings. Fine need aspiration cytology (FNAC) was performed which showed features suggestive of low-grade salivary gland tumour with differential diagnosis of low-grade mucoepidermoid carcinoma.

Computerized tomography (CT) scan of the neck, thorax, abdomen, and pelvis was performed for staging the tumour before surgery. The CT neck revealed homogenously enhancing multilobulated mass in the superficial lobe of the right parotid gland, measuring 4.2cm x 2.7 cm x 4.6cm, with foci of calcification seen within (Figure 1). The mass appears abutting masseter muscle anteriorly, trapezius muscle posteriorly and extending to the skin laterally without parapharyngeal extension medially. In addition, there was presence of enlarged cervical lymph nodes at levels II, III and V bilaterally. CT thorax, abdomen and pelvis showed no distant metastasis.

Subsequently the patient underwent right total parotidectomy and right modified neck dissection type 3. Intra-operatively the tumour involved superficial and deep lobes of the right parotid gland, measuring 10cm x 6cm, hard in consistency and attached to overlying skin laterally (Figure 2 and 3). The involved skin was removed together with the tumour. Furthermore the tumour was attached to the lower branch of the facial nerve and there was presence of multiple lymph nodes from level I to V Post-operatively the patient developed right facial nerve palsy, House Brackman grade III, otherwise no other complication. The facial nerve palsy fully recovered after six months.

Histopathology examination (HPE) of the tumour showed features suggestive of SC, circumscribed to the infiltrative and lobulated pattern of growth. It

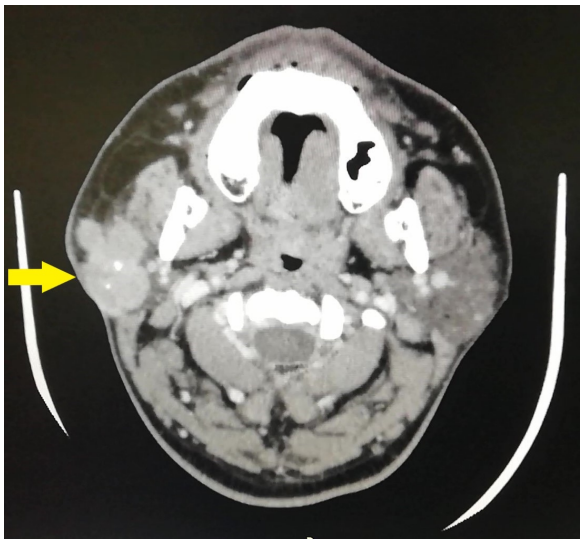

Figure 1 *CT neck shows homogenously enhancing multilobulated mass in superficial lobe of right parotid gland, measuring 4.2cm x 2.7 cm x 4.6cm, with foci of calcification. The mass appears abutting masseter muscle anteriorly, trapezius muscle posteriorly and extending to skin laterally without parapharyngeal extension medially.*

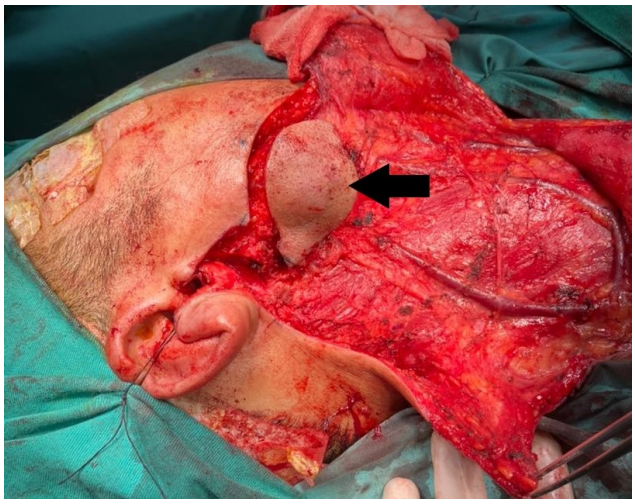

Figure 2 *Intra-operative picture show subplatysmal flap is raised and the tumour with involved overlying skin (arrow) plan to remove together. Lower part of neck is exposed for right modified radical neck dissection type 3.*

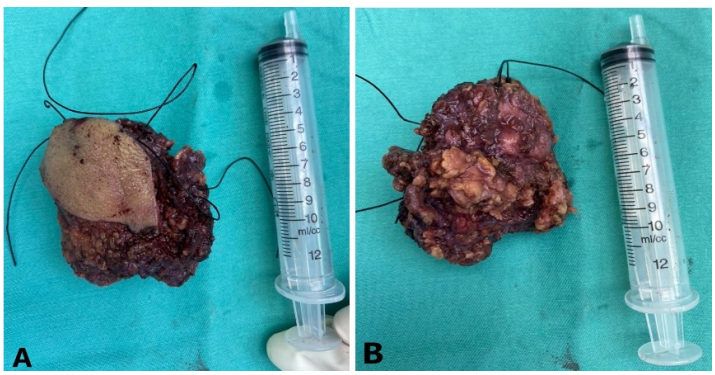

Figure 3 *Tumour in superficial lobe of parotid with involved skin, measuring 10x6cm (A) and tumour in deep lobe of parotid gland, measuring 12 x 6cm (B) were removed, tag with string and sent for histopathology examination.*

was displayed in microcystic, follicular and papillary-cystic structures with luminal secretion (Figure 4A). The immunohistochemical stains against S100 (Figure 4B), mammaglobin (Figure 4C) and CK7 were all positive. There was presence of perineural invasion (Figure 4D) and deep margin, as well as subcutis, were involved. Other margins were close to the tumour. Surprisingly no malignant cells were detected in the deep lobe of the parotid and all levels of the right cervical lymph nodes (levels I to V). The patient was subsequently referred to the oncology team for adjuvant radiotherapy.

DISCUSSION

The diagnosis of salivary gland tumours is always challenging due to the nature of salivary tumours that have marked morphological diversity with some of them showing overlapping features, some subtypes are extremely rare and rapid changes in nomenclature and classification in recent years.[7] In addition, limited samples for microscopic examination and lack of certain laboratory tests also contribute to the difficulty.

SC is currently recognized as a new distinct entity of salivary gland carcinoma and accounts for less than 0.3% of all salivary gland tumours and 5% of all malignant salivary gland tumours.[5,6] Majority of cases were misdiagnosed as acinic cell carcinoma or adenocarcinoma previously.[6,8,9] With the advance in molecular biology test, SC showed the typical characteristic of translocation mutation t (12;15) (p13; q25) which results in the fusion gene ETV6-NTRK3, which is absent in other salivary glands neoplasms.[8,9]

It showed male predominance in most series and commonly occur at 40 to 50 decades of life[3,6,9], which is consistent with our case. SC is generally classified as a low-grade carcinoma that usually presented with a painless slow-growing mass.[3] However it may show some features to suggest a more aggressive lesion as compared to acinic cell carcinoma, like a higher rate of cervical lymph node involvement and distant metastasis as well as local recurrence.[8] There was skin infiltration in our patient and the mass was abutting on the masticator muscle resulting in pain and trismus. In addition, there was microscopically perineural invasion and close surgical margin. Although the CT scan showed the presence of multiple cervical lymph nodes, HPE has proven no regional metastasis.

Due to the differences, thus it is important to differentiate the type of diseases to properly plan the management. FNAC is usually the first investigation of choice due to its generally good safety profile, low tumour seeding and high diagnostic accuracy.[10] However the clinical usefulness of FNAC in parotid gland lesions should be assessed

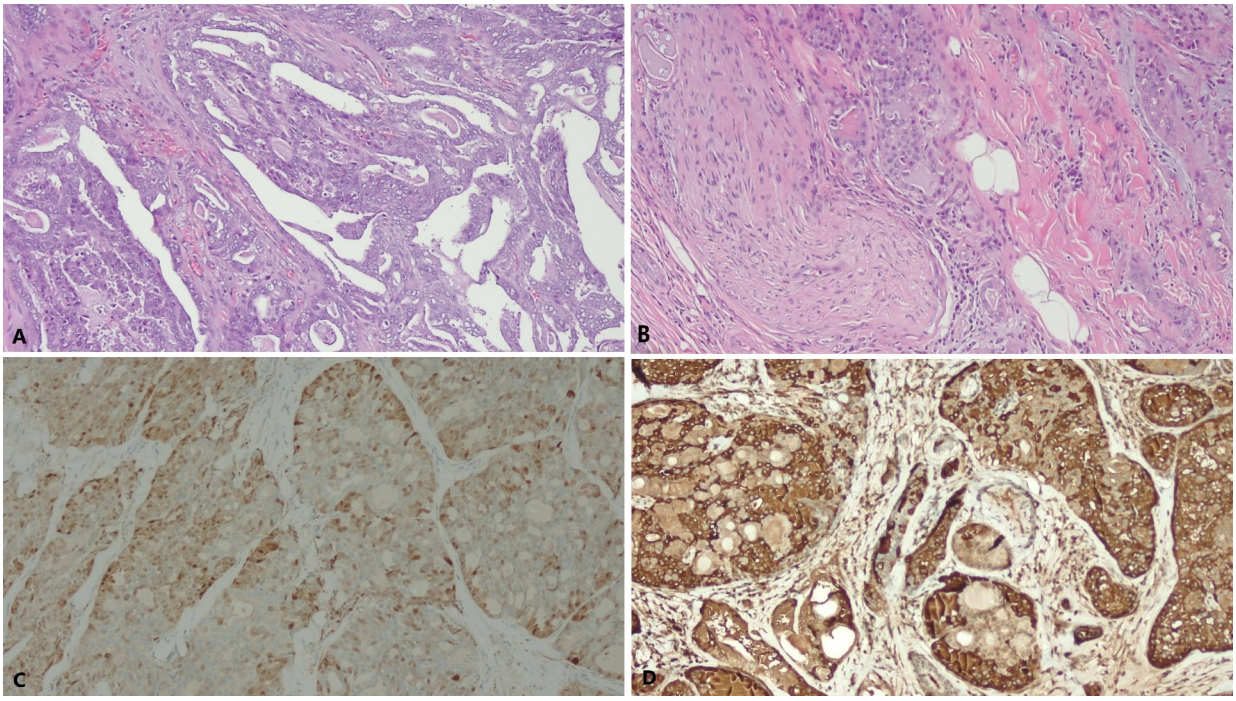

Figure 4 *HPE of the tumour shows circumscribed to infiltrative to lobulated pattern of growth, composed of microcystic, follicular and papillary-cystic structures with luminal secretion, and intracytoplasmic granules without zymogen granules, H&E, x200 (A). Immunohistochemical stains show positivity for S100, x100 (B) and mammaglobin, x100 (C). Tumour tissue invading into the perineural space surrounding a nerve, H&E, x100 (D).*

based on case-by-case and depend on local diagnostic performance, due to its wide variability of accuracy (sensitivity 52-100%, specificity 67-100%).[11] The accuracy varies depending on the experience of the FNAC operator, use of rapid onsite evaluation, cytologic preparation, the diagnostic experience of the cytopathologist, reporting terminology and characteristics of the salivary gland tumours.[12] Recently Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) has been developed to help standardize reporting system for salivary gland cytology, provide evidence-based risk stratification, guide in management and improve the communication between clinicians and pathologists.[13,14] Although the FNAC failed to provide an exact diagnosis consistent with the final HPE result in our case, it still gave important information that the lesion was malignant.

The gold standard investigation to diagnose SC is fluorescence in situ hybridization which can identify typical characteristic molecular alteration of t(12;15) (p13;q25) translocation.[9] This translocation that results in the fusion of genes ETV6 and NTRK3 will activate a signalling pathway leading to cell proliferation and neoplastic transformation is not seen in other salivary gland carcinomas. However unfortunately, some of the centres like ours are not well-equipped with this molecular test. A combination of histopathology study and immunohistochemical profile is believed to be sufficient for diagnosis in some typical cases.[9,15] Histopathologically SC has apocrine secretory epithelium morphology, papillary-cystic or microcystic pattern, abundant PAS-positive eosinophilic secretion, and absence of basophilic zymogen granules. Mammaglobin and S100 protein are among basic immunohistochemical profiles that suggest SC if positive.

The mainstay of treatment for parotid SC is parotidectomy, with or without neck dissection and adjuvant radiotherapy or chemotherapy depending on local disease extension and distant metastasis.[5,6,8] The principle of treatment is almost similar to other types of parotid carcinoma. The major difference is the presence of a promising alternative medical treatment with tropomyosin receptors kinase antagonists like crizotinib, entrectinib and larotrectinib, although still at the clinical trial level.[6]

CONCLUSION

SC is a newly recognized distinct entity of salivary gland malignancy in which most of cases were formerly misdiagnosed as acinic cell carcinoma or adenocarcinoma. Due to the different clinical characteristics and microscopic and molecular features, clinicians and pathologists should be alert to the existence of this entity. Surgery is still the mainstay of treatment, however there is promising alternative medical treatment with tropomyosin receptor kinase antagonists. Our case highlights a more aggressive form of SC which need post-operative adjuvant radiotherapy and challenges in diagnosis in a centre with limited laboratory resource.

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