CASE REPORT

ETV6-NTRK3 positive mammary analogue secretory carcinoma of the salivary gland: A case report and literature review

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Abstract

Mammary analogue secretory carcinoma (MASC) of the salivary gland is an extremely rare salivary gland tumour. It shows the same morphological, immunohistochemical and molecular features as that of the secretory carcinoma of the breast, making it a diagnostic enigma. Here, we report a case of ETS variant transcription factor 6 (ETV6)—neurotrophic receptor tyrosine kinase 3 (NTRK3) fusion gene positive MASC. A 59-year-old woman presented to our hospital with a mass on the right cheek. Computed tomography (CT) showed a nodular shadow in the right mandibular region, and the post-operative pathological diagnosis was confirmed as MASC (pT1N0M0). Immunohistochemical staining showed that the tumour cells were positive for pan-TRK, mammaglobin, and S-100. Fluorescence in situ hybridisation (FISH) confirmed the diagnosis.

ETV6 gene translocation and ETV6-NTRK3 gene fusion, but MET gene translocation was negative. Immunohistochemistry and genetic analysis are important tools to differentiate MASC from its morphological mimickers. The treatment approach for MASC has not been well defined or standardised, necessitating further studies to develop evidence-based guidelines.

Keywords: Salivary glands, Mammary analogue secretory carcinoma, ETV6-NTRK3 fusion.

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Introduction

Mammary analogue secretory carcinoma (MASC) is an extremely rare malignant salivary gland tumour, accounting for less than 0.3% of all salivary gland tumours, which was officially recognised as a separate entity in the fourth edition of the World Health Organisation classification of head and neck tumours in 2017.[1] The histological, immunohistochemical, and molecular features of MASC are similar to those of the secretory carcinoma of the breast.[2] Most cases of MASC are genetically specific with *t*(12; 15)(*p*13; *q*25) chromosomal translocation, resulting in ETS variant transcription factor 6 (ETV6) - neurotrophic tyrosine receptor kinase 3 (NTRK3) fusion gene.[3] This mutation is not identified in other salivary gland tumours.[4] NTRK has been a remarkable therapeutic target, and the approval of NTRK inhibitors by the Food and Drug Administration (FDA) for various malignancies has significantly impacted current oncology treatment. The accurate detection of NTRK gene fusion becomes very important for possible targetted therapy. We report a case of MASC diagnosis based on morphologic, immunohistochemical, and genetic features, to enhance the knowledge about this rare entity.

Case Report

A 59-year-old woman presented to the First Affiliated Hospital of Dali University, Dali, China, on October 9, 2023. She had no history of previous medical consultations. Three years ago, the patient first noticed a "pea-sized" mass on her right cheek, which had gradually increased to the size of a quail egg in recent years. The patient's spirit, diet, and sleep were not affected by the mass. The right side of her face was slightly swollen, the skin was not red, and there were no obvious scars, fistulas, and ecchymosis. There was no pain or noise when pressing bilateral temporomandibular joint, and the degree of mouth opening was not limited. A pink mass, about 3x2cm in size, was seen in the patient's mouth that was slightly painful to press. Computed tomography (CT) showed a circular mixed density shadow in the right mandibular region. Contrast-enhanced scan showed irregular enhancement, but the cystic component was not enhanced (Figure 1A). The patient underwent resection of the buccal mass, which only removed the mass. Pathological examination of the mass was performed after the operation.

The tumour size was 2x1.5x1cm, and the cut surface was solid and grey-white. At low magnification, the tumour was divided by fibrous septa (Figure 1B). At high magnification, the tumour was microcystic and tubular, and the lumina was filled with eosinophilic secretions; abundant eosinophilic cytoplasm and oval vesicular nuclei were observed in the tumour cells, but mitotic figures were infrequent (Figure 1C). No vascular or perineural invasion was seen.

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Immunohistochemical staining showed that the tumour cells were positive for pan-TRK, mammaglobin, S-100, CK7, SOX-10, Vimentin (Figure 1D to I), CK8/18 and CK19, and the Ki-67 proliferation index was approximately 10%, but negative for P63, P40, GFAP, CD117, SMA, GCDFP-15, DOG1 and AR.

Alcian Blue-Periodic Acid-Schiff (AB-PAS) staining showed the presence of acidic mucin in the cytoplasm and intraluminal secretions (Figure 2A). Fluorescence in situ hybridisation (FISH) showed positive ETV6 gene translocation, ETV6-NTRK3 gene fusion, and negative MET gene translocation in tumour cells (Figure 2B to D).

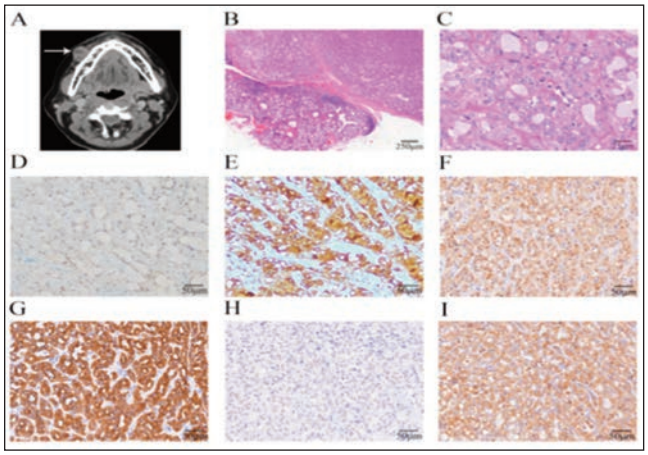

Figure-1: Radiological, histological and immunohistochemical examination of the tumour. (A) Computed tomography (CT) images of the neoplasm (arrow). (B) the tumour was divided by fibrous septa; magnification 40×. (C) the tumour was microcystic and tubular, and the lumina was filled with eosinophilic secretions; The tumour cells displayed abundant eosinophilic cytoplasm and oval vesicular nuclei, while mitotic figures were rarely observed; magnification 400×. Immunohistochemical analysis showed that tumour cells were positive for pan-TRK (D), mammaglobin (E), S-100(F), CK7(G), SOX-10 (H), and Vimentin (I), magnification 200×.

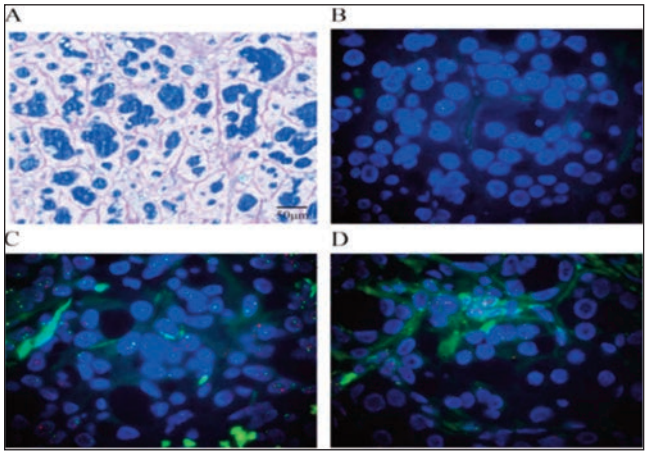

Figure-2: (A) Alcian Blue-Periodic Acid-Schiff (AB-PAS) staining showed the blue secretions, magnification 200×; B-C, fluorescence in situ hybridisation (FISH) showed that tumour cells were positive for ETV6 gene translocation (B) and ETV6-NTRK3 gene fusion (C), and negative for MET gene translocation (D), magnification 1000×.

Because only the mass was removed during the first operation, the patient was re-admitted for extended resection in November 2023. After this procedure, no residual tumour or lymph node metastasis was noted, and the tumour was finally diagnosed as MASC (pT1N0M0). The patient was treated with two cycles of PVF chemotherapy regimen (Cisplatin+Vincristine+Fluorouracil) in December 2023 and January 2024, respectively. As of August 2024, the patient is in good condition, with no recurrence or metastasis.

Discussion

The overall prevalence of MASC is extremely low, accounting for less than 0.3% of all salivary gland tumours.[5] The average age at diagnosis was 45.7 years, and it is more common in males.[6] At present, the pathogenesis of MASC is still unclear.

The tumour usually presents as an isolated, painless, rubbery tan mass with a well-defined border, growing slowly. The size of the mass ranges from 0.2 to 5.5 cm, with a mean size of 1.7 cm.[7] The tumour is divided by fibrous septa with areas of microcystic, tubular, papillary cystic and solid patterns, the tumour cells and the lumina contain abundant eosinophilic secretions. The tumour cells show low-grade oval vesicular nuclei, while atypia and mitoses are rarely observed, as well as necrosis and perineural invasion.[8-11] The eosinophilic secretions in the tumour cells and the lumina are positive for PAS, diastase-PAS (D-PAS) and AB-PAS.[11]

The tumour cells of MASC are strongly positive for S-100 and mammaglobin proteins, and the diagnostic sensitivity of both is as high as 95%, but they are not specific. MASC is also positive for cytokeratin, STAT5a and Sox10. However, it is negative for P63, DOG-1, SMA, and Calponin, and Ki-67 expression is generally low (<5%).8,9 Pan-TRK is a specific immunohistochemical marker for MASC, and its nuclear positivity has 100% specificity for indicating NTRK3 gene fusion and secretory carcinoma.[12] MASC needs to be differentiated from other diseases with similar histological features. The tumour cells of mucoepidermoid carcinoma (MEC) are positive for P63, and the CREB regulated transcription coactivator 1 (CRTC1)- mastermind like transcriptional coactivator 2 (MAML2) gene fusion is often positive.[13] The tumour cells of acinic cell carcinoma (AciCC) feature distinct blue-purple zymogen granules.[7] In addition, AciCC shows positive expression for DOG1, while the ETV6 - NTRK3 gene fusion is negative.[14] Salivary duct carcinoma (SDC) shows positive expression for AR, and adenoid cystic carcinoma (ACC) shows positive expression for CD117.

The typical molecular genetic variation of MASC is the rearrangement of ETV6 gene, the most common of which is the ETV6-NTRK3 fusion due to *t*(12; 15)(*p*13; *q*25) chromosome translocation, resulting in constitutive activation of a tyrosine kinase that promotes tumourigenesis by continuously promoting cell proliferation and improving cell survival.[15] The mitogenic pathway of Ras-MAP kinase and phosphatidylinositol-3-kinase-Akt pathway may also be activated during this process.[2] ETV6-NTRK3 fusion has been identified in some other tumours, such as acute myeloid leukaemia, congenital fibrosarcoma, and congenital mesoblastic nephroma.[10,16] However, except for MASC, ETV6-NTRK3 fusion has not been noted in other salivary gland tumours.[4] In recent years, more novel genetic alterations in MASC have been identified. In 2018, Skalova et al.[17] found ETV6-RET fusion in MASC, and Rooper et al.[18] reported ETV6-MET fusion in a highly aggressive MASC case. In 2019, Guilmette et al.[19] revealed a novel ETV6-mastermind like transcriptional coactivator 3 (MAML3) fusion present in a case of MASC with concurrent ETV6-NTRK3 fusion. In 2020, concurrent identification of novel EGFR-SEPT14 fusion and ETV6-RET fusion in a MASC was reported by Black et al.[10] It should be emphasised that negative ETV6-NTRK3 fusion does not exclude the diagnosis of MASC.[20]

At present, the treatment of MASC has not been defined or standardised.[15] The main treatment for MASC is surgical resection. Yassin-Kassab et al.[8] proposed that post-operative radiotherapy (PORT) is recommended for patients with inadequate resection, resection margins less than 5mm, perineural invasion, tumours categorised as T3 to T4, or cervical lymph node metastasis. The United States FDA and the European Medicines Agency (EMA) have approved two TRK inhibitors, Larotinib and Entrutinib, for the treatment of cases with NTRK gene fusion.[3] Some patients with MASC can benefit from TPK inhibitors.[21] C-Met inhibitors, Cabozantinib or Crizotinib, are potential treatment options for cases with ETV6-MET fusion.[10] Most MASC patients have favourable prognosis.[8] MASC is usually low-grade and indolent, with a low to moderate risk of recurrence, lymph node metastasis and distant metastasis.[22] However, it remains intrinsically malignant, with high-grade transformation in a small number of cases. Currently, there are no established pathological criteria for high-grade transformation. Tumours with high-grade transformation often demonstrate the following morphological features: a trabecular growth pattern with irregular solid nests, nuclear pleomorphism, distinctive nucleoli, high mitotic activity, an elevated Ki-67 labelling index, and necrosis.[4,23] Necrosis often suggests higher aggressiveness and worse prognosis.[8] Therefore, MASC patients need to be followed up closely after surgery.

Conclusion

Current evidence regarding the management of MASC is still lacking, and more studies are warranted to establish guidelines. This study reports a rare case of ETV6-NTRK3-positive MASC, further confirming that immunohistochemistry and genetic analysis are important tools to differentiate MASC from its morphological mimickers, supporting clinical diagnosis, treatment planning, and prognosis assessment. Additionally, this case enriches relevant clinical data, and provides references for future research.

Informed consent: Consent for publication was obtained from the patient.

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Author Contribution:

YY & LZ: Concept, design, data acquisition, analysis, interpretation, drafting, revision and final approval.

YP: Concept, design, data acquisition, analysis, interpretation and final approval.

BG: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.