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CASE REPORT

Synchronous Parotid (Mammary Analog) Secretory Carcinoma and Acinic Cell Carcinoma: Report of a Case

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Abstract

Mammary analogue secretory carcinoma (MASC) is a recently described low-grade salivary gland malignancy with histologic, immunohistochemical and molecular similarities to secretory carcinoma of the breast, including a specific t(12;15)(p13;q25) resulting in an ETV6–NTRK3 gene fusion. Ultrasound and magnetic resonance imaging frequently document a macrocystic structure. The main differential diagnosis of secretory carcinoma is with low grade acinic cell carcinoma (AciCC). The two can be differentiated with immunohistochemical stains for S100, mammaglobin, carbonic anhydrase VI and DOG-1; the identification of the specific translocation can help to characterize non-typical cases. We report a unique case of synchronous MASC and AciCC presenting in a parotid gland and discuss the implications of the correct identification of the two tumors.

Keywords MASC · Salivary gland tumor · Cystic carcinoma · Parotid · Acinic cell carcinoma

Introduction

Mammary analogue secretory carcinoma (MASC) of salivary glands was first described by Skalova et al. [1]; since then, more than 225 cases have been reported. In the 2016 WHO classification of head and neck tumors [2] the tumor is classified as secretory carcinoma and included among low-grade malignant neoplasms with favorable prognosis. MASC have striking morphological, immunohistochemical and molecular similarities to secretory carcinoma of the breast, including a tumor-specific t(12;15)(p13;q25) translocation resulting in ETV6–NTRK3 fusion [3–6]. After the initial description, some cases have been reported lacking the ETV6–NTRK3 fusion [7] or carrying ETV6–RET translocations [8]. The authors suggest that these atypical molecular features may be associated with more aggressive histological features and less favorable clinical outcome.

Ultrasound (US) and magnetic resonance imaging (MRI) of MASC frequently document a macrocystic structure. This feature is shared by other benign and malignant salivary gland neoplasm including pleomorphic adenoma, Warthin's tumour, mucoepidermoid carcinoma and acinic cell carcinoma [9]. Ultrasound-guided fine-needle aspiration biopsy (FNAB) is an appropriate adjunct to imaging, but a specific histotype definition of low-grade carcinomas is difficult to obtain on cytological samples [10]. The main differential diagnosis of MASC, both on cytology and histology, is low grade acinic cell carcinoma (AciCC), which shares MASC heterogeneous histopathological architecture. Fluorescence in situ hybridization (FISH) identification of the ETV6–NTRK3 translocation confirms MASC diagnosis [11, 12], but the tumor immunohistochemical profile (S100 and mammoglobin expression, negativity for DOG1) is sufficient to accurately diagnose the majority of cases [13, 14]. Moreover, carbonic anhydrase VI is a promising new marker which can further strengthen MASC immunophenotyping and facilitate establishing the diagnosis without molecular genetic data [15].

We report the unusual occurrence of two distinct, synchronous carcinomas developing in the same parotid gland,

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diagnosed as mammary analogue secretory carcinoma and acinic cell carcinoma.

Case Report

A 64-year old female presented with a 3 year history of left-sided face painless swelling. US examination (Fig. 1a) documented an hypoechogenic lesion (19 × 16 mm), with regular margins and an eccentric fluid gap; a 1 cm lymphnode was also recognised in the deep portion of the gland. The lesion increased slowly over the following 3 years, when MRI scan (Fig. 1b, c) showed a contrast-enhancing mass with liquid content. US-guided FNAB showed abundant, morphologically uniform salivary epithelial cells with mild cytological atypia, suggestive for a low-grade salivary neoplasm (Fig. 1d). A partial left parotidectomy was performed with radical excision of the cystic lesion; furthermore, 1 cm solid nodule was identified and removed from the inferior portion of the deep lobe. The second nodule was clearly distinct from the previous one; the distance between the two was more than 2 cm. The examination of the surgical sample showed a 3 × 2 × 1.8 cm cystic hemorrhagic nodule, lined by single or multiple layers of epithelial cuboidal cells of medium size with round, regular nuclei, focally forming microcystic space (Fig. 2a, b, e). Tumor cells were positive for low and high molecular weight cytokeratins, vimentin, mammaglobin (Fig. 2d) and S100, and negative for p63, DOG1 (Fig. 2c), smooth muscle actin, CD117, and androgen receptor. ETV6 gene translocation was present in 53% of tumor cells by FISH (Fig. 2f). The gross examination of the deep parotid lobe sample showed a solid white nodule (0.6 × 0.5 × 1 cm). Microscopically it was recognized as an intraparenchymal lymphnode (Fig. 3a), with diffuse infiltration of poorly formed acinar aggregates of epithelial cells. Tumor cells showed abundant PAS-D + cytoplasmic zymogen granules (Fig. 3b, c), membranous and cytoplasmatic expression of DOG-1 (Fig. 3d), and absence of p63, smooth muscle actin, and S100 expression. ETV6 gene was not translocated. This profile was consistent with an acinic cell salivary gland carcinoma. Both lesions were completely resected. No evidence of disease was found at 6 month follow up.

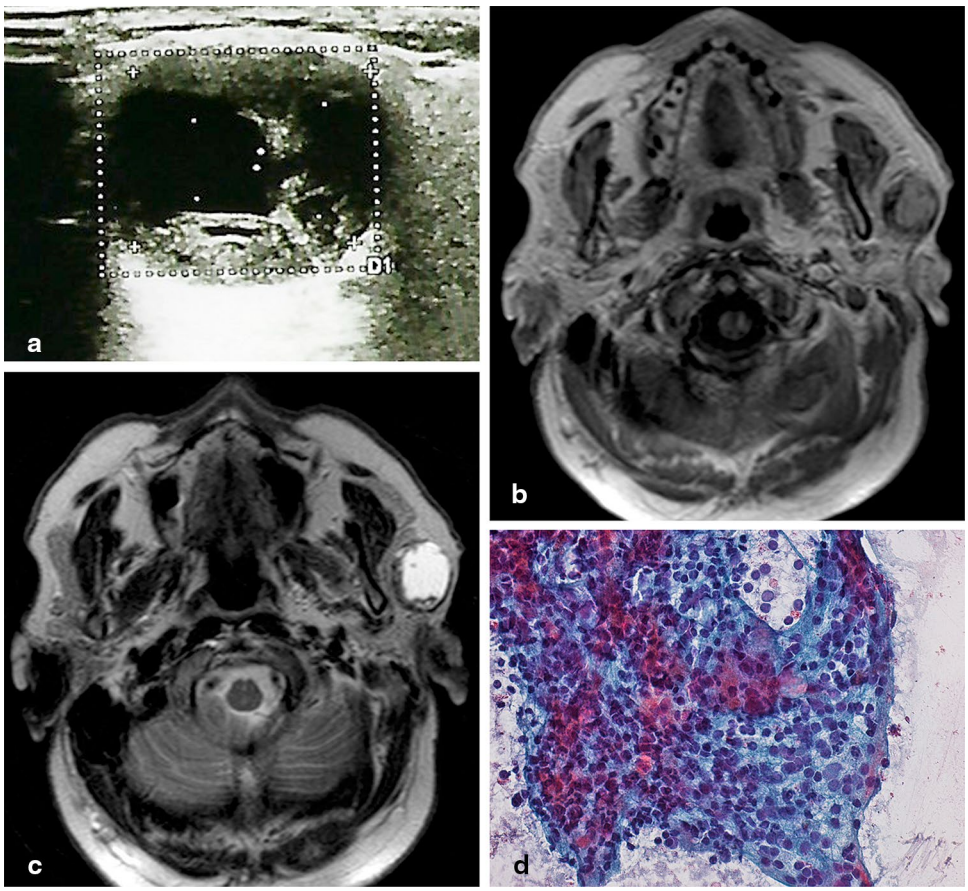

Fig. 1 Ultrasound examination **a** showed an hypoechogenic lesion with regular margins and eccentric fluid gap; T1 (**b**) and T2 (**c**) magnetic resonance imaging documenting a contrast-enhancing mass of the left parotid gland with liquid content; US-guided FNAB (**d**) showed sheets of salivary epithelial cells, morphologically uniform and with mild cytological atypia, suggestive for a low grade salivary neoplasm

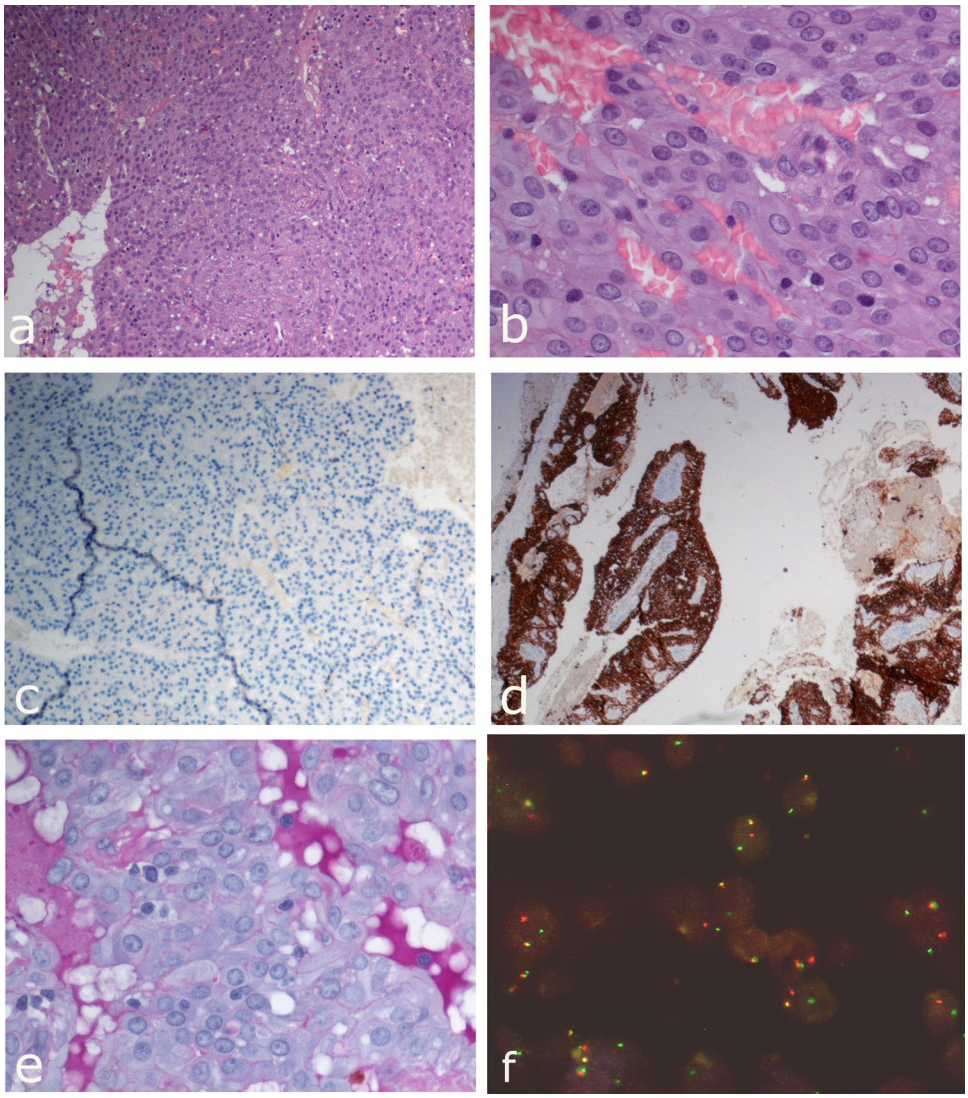

Fig. 2 Histological features of MASC: the mass was centrally cystic (**a**), and composed of polygonal cells with mild atypia (**b**), negative DOG-1 (**c**), positive for mammoglobin (**d**) and negative for PAS stain (**e**); ETV6 gene translocation with break-apart FISH (**f**)

Discussion

MASC are known to have heterogeneous cytomorphological and architectural features [16]. A macrocystic structure is frequently recognized at instrumental and gross examination, and is shared by several other benign and malignant salivary gland neoplasms (Table 1). In particular, retrospective studies showed that, before the recognition of MASC, most cases were classified as AciCC [17]. The final diagnosis requires histopathological analysis, histochemical stain and immunohistochemical study: MASC are typically positive for S100 and mammaglobin, whereas DOG1 is a specific AciCC marker [13]; PAS-D positive zymogen granules are also typical of AciCC. The identification of ETV6 or less common gene translocation can be useful in cases with non-typical features. The case reported here is unique in that synchronous MASC and AciCC were present in the same gland. Synchronous tumors of different histological types are extremely rare in the salivary glands [18]: in the parotid, they account for less than 0.3% of all salivary neoplasms. The most common dual pathology reported is Warthin's tumor and pleomorphic adenoma, while malignant tumors are uncommon. Reported malignant synchronous tumors of the parotid consist mostly of single nodules with divergent carcinoma histologies [19]. Most reported separate nodules with different histologies in the same gland include on the contrary at least one benign lesion (pleomorphic adenoma or Warthin's tumor), while double malignant tumors are exceedingly rare [20]. The other peculiarity of this case is the development of a primary salivary gland carcinoma within an intraparotid lymph node. Ectopic salivary tissue is common in intraparotid and periparotid lymphnodes, and sometimes can give origin to tumors. Warthin tumor is a relatively common finding in nodal ectopic salivary gland tissue and in intraparotid lymph

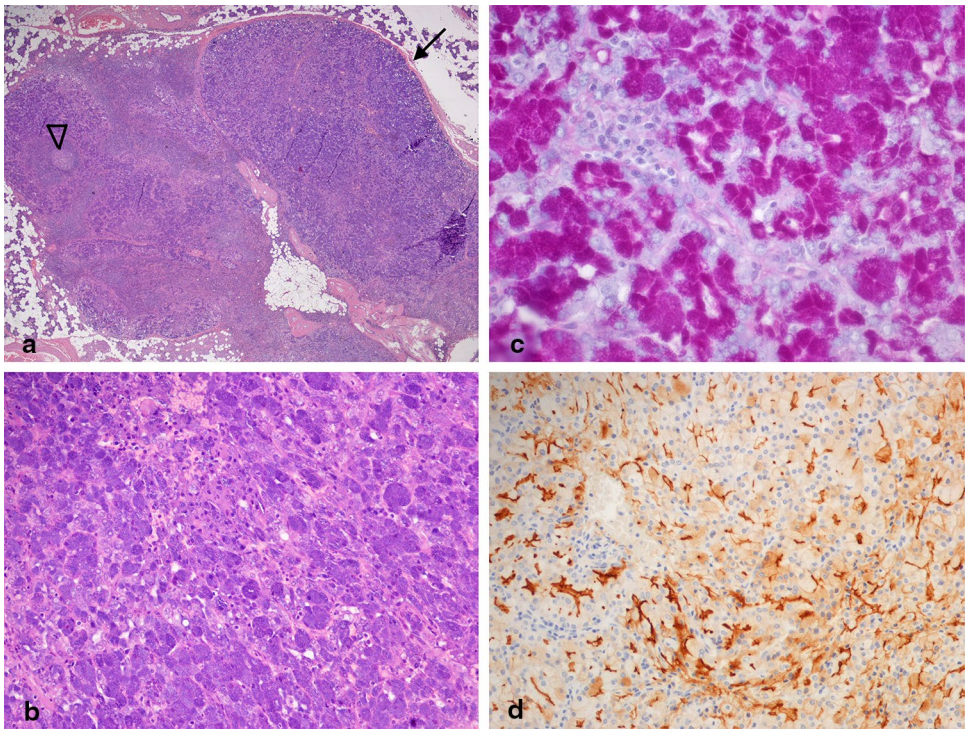

Fig. 3 Histological features of the deep lobe nodule. The low-power view **a** shows a thin capsule (arrow), a hilar region (lower right corner), and a lymphoid follicle (arrowhead), consistent with an intraglandular lymphnode. The lymphnode was infiltrated by mildly atypical large cells with a basophilic cytoplasm (**b**), containing PAS + zymogen granules (**c**), positive for DOG-1 (**d**)

Table 1 Differential diagnosis between cystic salivary gland carcinomas

Tumor	Cytomorphology	Architecture
(Mammary analogue) secretory carcinoma	Uniform polygonal cells, mild atypia	Papillary-cystic, solid and microcystic
Cystadenocarcinoma	Cellular heterogeneity (cuboidal, tall columnar, clear to oncocytic cells)	Evenly thin lining with large papillary projections
Low-grade mucoepidermoid carcinoma	Cellular heterogeneity (squamoid differentiation, goblet cells, intermediate cells)	Cobblestone-like irregular luminal projections
Warthin tumor	Uniform bland oncocytic polygonal cells	Broad papillary structures with lymphoid stroma
Cystadenoma	Bland cuboidal to polygonal cells, occasional mucous or oncocytic differentiation	Variable papillary projections or septa
Intraductal papilloma	Uniform cuboidal to polygonal cells	Complex papillary ramifications with thin fibrovascular cores

nodes [21]. Although rare, malignant transformation of the ectopic salivary tissues is possible. In literature there are few reports of salivary malignant tumor developing primarily in intraparotid lymphnodes [22–25] including rare AciCC [26–28]. The main diagnostic issue in this rare setting is excluding a nodal metastasis form a salivary gland primary. To our knowledge, this is the first report of synchronous parenchymal and nodal parotid carcinomas with different histotypes (MASC and AciCC). The two tumors have probably developed following independent neoplastic transformation, considering the absence of risk factors as previous irradiation. This report highlights the importance of a complete histochemical, immunohistochemical and molecular characterization of low grade salivary neoplasms with monomorphic acinic-like morphology. In this case, we could recognize the two lesions as independent, and stage both as stage 1 (pT2N0M0 and pT1N0M0), rather than stage 3 (pT2N1M0).

Mammary analogue secretory carcinoma is currently considered and treated as a low-grade carcinoma with overall good prognosis [29–31]. As compared with AciCC, the clinical outcomes are very similar, although MASC is considered slightly more aggressive [3]. Local recurrences, high-grade transformation, as well as regional lymphnode and distant metastasis and disease-related death have been reported [32]. The recent identification of MASC and the low number of cases described limits the definition of prognostic and predictive factors. ETV6–NTRK3 translocation may represent a therapeutic target for chimeric tyrosine kinase (TK) inhibitors in aggressive cases. ETV6–NTRK3-translocated acute

and chronic leukaemias occasionally respond to TK inhibitors [33]. Furthermore, in-vitro studies established a relationship between the transforming activity of ETV6–NRTK3 and the insulin-like growth factor receptor (IGFR1) pathway in breast secretory carcinoma [34]. At present, radical surgery is the first treatment choice for MASC, similarly to other salivary gland neoplasms. Local recurrence can result from incomplete excision and adjuvant radiotherapy is recommended in the case of partial resection. In the future, the identification of MASC could also become crucial for accurate patient selection for personalized therapies targeting TK or IGFR1.

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