CASE REPORT

ETV6–NTRK3-positive parotid mammary analogue secretory carcinoma: a case report

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Abstract

Introduction: Mammary analogue secretory carcinoma (MASC) is a recent discovered entity of salivary glands tumors, reported for first time in 2010. The presence of a translocation encodes the ETS variant transcription factor 6–neurotrophic tyrosine receptor kinase (ETV6–NTRK3) gene fusion differences MASC from other tumors. Case presentation: A 68-year-old male showed a non-painful right parotid enlargement, came from dermatology service, and followed by some facial squamous cell carcinomas. A computed tomography (CT) scan showed a 1.7×1.6 cm right parotid enlargement in superficial lobe. The patient underwent a right superficial parotidectomy. The final pathology confirmed the presence of ETV6–NTRK3-positive MASC. Complete right deep parotidectomy and functional cervical emptying were performed. Discussions and Conclusions: It is necessary to establish an appropriated differential diagnosis between salivary gland tumors. MASC is a low-grade malignancy cancer that sometimes can evolve to a high-grade tumor that might produce local and distance dissemination. Most times, these tumors are only treated by surgical resection and evaluating by a multidisciplinary team the need of more treatments. In our case, the patient showed a primary parotid tumor, removed surgically with free edges, and being identified as MASC. We decided to underwent neck dissection and discovered a second MASC focus on cervical salivary gland; however, there was no nodal dissemination. The patient remains disease-free after 14 months from last surgery. It is important to keep studying genetic therapy targets to ETV6–NTRK3 to obtain a new therapy line to treat those cases that require.

Keywords: parotid, salivary, cancer, head and neck, case report.

Introduction

Mammary analogue secretory carcinoma (MASC) is a recently discovered tumor in the differential diagnosis of salivary tumors, firstly described by Skálová et al. in 2010 [1]. MASC appears almost in same proportion in both genders, although some studies may give male predominance. The average age of presentation is around mid-40s [2]. Most times, it is a slow-growing non-painful tumor with years of development before causing clinical symptoms [1–4]. This recently discovered tumor were underdiagnosed as other tumors as salivary acinic cell carcinoma (AcCC). The difference between these two entities is the presence of a t(12;15)(p13;q25) translocation that encodes ETS variant transcription factor 6–neurotrophic tyrosine receptor kinase (ETV6–NTRK3) gene fusion, present in MASC and absent in AciCC [1–5].

Aim

We present a patient with non-symptomatic parotid tumor who underwent conservative superficial parotidectomy followed by unilateral functional cervical dissection after pathological anatomy results.

Case presentation

We evaluate a 68-year-old male patient with a right non-painful parotid enlargement of months of evolution. As previous medical history, he had hypertension, moderate prostatic syndrome, chronic renal insufficiency (CRI) and cardiac failure. He was under follow-up by plastic surgery and dermatology for some facial squamous cell carcinomas, waiting for surgery. He had had a calcaneal fracture, which required surgery. He took some medications: Candesartan/Hydrochlorothiazide, Aceclofenac and Salbutamol. No toxic habits and no drug allergies.

In physical examination, there was an enlargement in right parotid at the mandibular angle, around 2 cm size, hard and not adhered to deep tissue. He did not have facial paralysis and there was no lymphadenopathy.

In first place, two coarse needle biopsies reported the presence of clear cells, advising the exeresis of the tumor. After that, a computed tomography (CT) scan with intravenous contrast showed a 1.7×1.6 cm right parotid enlargement in the superficial parotid lobe that extended to the subcutaneous fat. It also showed two millimetric local nodes that may fit with intraparotid nodules. Furthermore, it showed an 8 mm lymphadenopathy in the right IIA cervical level.

According to the findings, the patient was introduced in our Hospital Tumor Committee for head and neck cancers, where we decided to underwent a right superficial lobe parotidectomy (Figure 1). A final pathology showed a 1.5×1.3 cm capsuled lesion with some cysts inside between 0.4 cm and 0.6 cm...
The lesion had free edges and was positive for S100 and mammaglobin. Furthermore, there was a low Ki67 index and few p53-positive cells. Fluorescence in situ hybridization (FISH) study indicated a pathogenic translocation between exon 4 of ETV6 and exon 14 of NTRK3, which had been described in MASC (Figure 2).

**Figure 1** – Images obtained from the right superficial lobe parotidectomy: (A) Upper lateral vision of the patient in the surgery room; the parotid tumor has been marked, as well as the incision zone; (B) Surgical zone exposing the different branches of the facial nerve; the superficial lobe of the parotid, including the tumor, was hold with Allis forceps; (C) Surgical resection piece including superficial lobe of the parotid and the tumor; (D) Final result after closing the surgical zone by planes.

**Figure 2** – (A and B) The tumor showed a lobulated pattern with fibrous septa. It was composed by structures, sometimes papillary, with tubules and microcysts, with eosinophilic discharge. There were not many atypical cells. (C–F) Using immunohistochemistry techniques, it can be observed that the sample was positive for mammaglobin (×10) (C) and S100 (×40) (D). There were many nuclei positive for estrogen receptors (×40) (E). Furthermore, pan-NTRK (×40) (F) was positive with immunohistochemistry. HE staining: (A) ×10; (B) ×40. HE: Hematoxylin–Eosin; NTRK: Neurotrophic tyrosine receptor kinase.
According to the results, he was reevaluated and suggested to undergo functional cervical emptying and complete deep parotidectomy, which was successfully undergone with no secondary complications. The pathology analyzed the cervical dissection piece and reported 49 lymph nodes without malignancy evidences, but the ipsilateral submandibular gland was affected with MASC and free edges. FISH reported a positive result for ETV6–NTRK3. There were no malignancy evidences in the deep parotid. The patient remained asymptomatic 14 months from the last surgery.

**Discussions**

In 2010, Skálová et al. discovered MASC as a new diagnosis in salivary tumors with histological features similar to those that appear in secretory breast carcinoma [1]. From the literature, this cancer affects the parotid gland in about 65–75% of cases, the submandibular gland in about 4–9% of cases and can also involve other sites, such as soft palate, base of the tongue and lip [2, 3]. Nowadays, the criteria that included this histopathological features, immunohistochemistry techniques and clinical manifestations have been described [4–7].

On gross inspection, most time MASC is a lonely, well-surrounded and unencapsulated tumor. Some important histological characteristics of this cancer include eosinophilic vacuolated cytoplasm, intracellular colloid-like secretions positive for Periodic Acid–Schiff (PAS) staining, and positive immunostaining for S100 and for mammaglobin [7, 8]. As previously said, the defining cytogenetic characteristic of this type of cancer is the presence of the ETV6–NTRK3 t(12;15)(q13;q25) translocation, analyzed by FISH or polymerase chain reaction (PCR) [8–10]. It is rare to find aggressive features but, in some cases, it has been reported the presence of extracapsular extension and perineural invasion [11].

In 2015, Majewska et al. described a seven cases study with MASC introducing main clinical features in these patients: most of them were indolent with a slowly growing mass [7]. It can also appear some symptoms as accelerated swelling, pain, or skin infiltration [8]. Fine-needle aspiration (FNA) may be useful to evaluate the characteristic of the lesion but, most times, is not allowed to provide a definitive result. However, some recent studies have shown that FNA obtained cells may undergo FISH analysis for ETV6–NTRK3 translocation [4, 12, 13]. Nonetheless, it is necessary to remove the tumor and the surgery piece must be evaluated by a pathologist, to obtain the diagnosis [2–4].

As said before, the differential diagnosis of MASC must be done between some other entities, such as AciCC, low-grade salivary duct carcinoma (LGSDC), high-grade salivary duct carcinoma (HGSDC) or mucoepidermoid carcinoma (MEC). AciCC is a tumor that presents so many pathological overlaps with MASC, but it typically presents basophilic cytoplasm containing PAS-positive zymogen granules [10]. Furthermore, AciCC has negative immunoreexpression of S100 protein and mammaglobin. But the most important feature is that there are no cases of ETV6 rearrangement in AciCC cancers [1–5]. HGSDC is not a typical entity in the differential diagnosis with MASC but, in high-grade MASC, it is useful to identify the cancer. Furthermore, HGSDC shows an amplified human epidermal growth factor receptor 2 (HER2) gene that has not been proved in MASC [10, 12, 13].

On CT scan, MASC has been described as a well-circumscribed enhancing lesion, with no spread to other tissues in most patients. On magnetic resonance imaging (MRI), it appears as a hyperintense and enhancing T1 lesion but an either hypointense or hyperintense T2 lesion [4].

Although MASC acts, most times, as a low-grade malignancy tumor with good prognosis, it can evolve to a high-grade tumor [4]. In comparison with AciCC, according to Chiosea et al., MASC showed a mean survival of 92 moths, whereas AciCC showed a mean survival of 121 months, with no statistical differences. MASC patients were more likely to present higher values of tumor (T) stage at diagnosis; furthermore, the presence of regional nodal disease at the diagnosis was higher in MASC patients [14, 15].

MASC is treated as a low-grade malignancy tumor in most cases. The common standard of treatment is radical surgical resection. It may be indicated the administration of post-operative radiotherapy (PORT) in some cases: close margin (<5 mm), incomplete resection, perineural invasion, T3–T4 tumors [4, 16, 17]. There are no uniform criteria established for nodular disease, but it depends on T stage, histology, and location. Furthermore, some authors like Terhaard et al. recommend neck dissection in all patients with high-risk criteria [17].

One of the most important features of MASC is the capability of apply genetic targeted therapy. The well-defined ETV6–NTRK3 translocation typical of this tumor allows the possibility of use it as a target in treatment. Some studies have indicated the possibility that Entrectinib, a tyrosine kinase [tropomyosin receptor kinase (TRK)] inhibitor of TRKA/B/C, may be useful. In fact, in some leukemia cases, the fusion of ETV6 sometimes respond to TRK inhibitors [1, 3, 5, 18–21]. Furthermore, some in vitro studies of mammary stem cells (SCs) have reported some evidences that insulin-like growth factor receptor-1 (IGF1R) inhibitors may be a target in the treatment by blocking ETV6–NTRK3 translocation oncogenesis [18, 22].

From 2015 to 2019, we underwent surgery a sample of 263 craniocervical glands affected by cancers. According to our data, pleomorphic adenoma (114 glands, 43.35%), Warthin tumors (89 glands, 31.55%) and lymphomas (11 glands, 4.2%) were the most common tumors identified after the surgery. MASC (two glands, 0.76%), however, was only present in our patient by two times: affecting the parotid gland in the beginning and the submandibular gland, being identified as two primary MASC focus. Thus, not only demonstrate the low incidence of MASC but its recent impact in craniocervical surgery.

In our patient, in first time we remove surgically the primary tumor (superficial lobe parotidectomy), with free edges and obtaining a result of right parotid MASC. With this result, our Tumor Committee decided to complete the parotidectomy and underwent the patient to an ipsilateral neck dissection, resulting in no lymph nodes affected but an ipsilateral submandibular gland affected by a regional MASC dissemination, removed with free edges. After that, our patient kept under clinical and imaging following with no evidences of malignancy after 14 months from the surgery.

**Conclusions**

We have presented a patient with non-symptomatic right parotid tumor who underwent right superficial lobe parotidectomy in first place, followed by a complete deep lobe parotidectomy and ipsilateral functional cervical
emptying with the diagnosis of MASC. A second focus was identified in ipsilateral submandibular gland, with no lymph nodes affected, suggesting a second primary MASC. No chemotherapy or genetic therapy was applied on this patient. Our patient is disease-free for 14 months. It is important to realize that MASC has been underdiagnosed from years ago but, recently, it is appearing as a new entity that we must consider in the differential diagnosis of head and neck cancers. This report aims to keep studying some therapeutic line that allows an appropriate treatment of this cancer when it is required.

Conflict of interests
The authors declare that they have no conflict of interests.

Ethical standards
We declare and certificate that the procedures and experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000, as well as the national law.

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