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CASE REPORT

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HER2-positive metastatic, parotid salivary duct carcinoma treated with a trastuzumab/pertuzumab-based chemotherapy: A case report

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Abstract

This case highlights the rare entity, salivary duct carcinoma (SDC), which is difficult to diagnose and manage. It is the first published case of a metastatic, HER2-positive parotid SDC successfully treated by a dual anti-HER2 treatment associated to a chemotherapy.

KEYWORDS

duct carcinoma, HER2, parotid, pertuzumab, trastuzumab

1 | INTRODUCTION

Firstly described by Kleinsasser,[1] salivary duct carcinoma (SDC) is an aggressive tumor representing 1%-3% of all salivary gland malignancies.[2] Several histological subtypes have been reported.[2-6] Many clinical and histological factors, including neck involvement, tumor size, older age, and the micropapillary and sarcomatoid variants, seem to be associated with a poor prognosis.[2-13] SDC can develop de novo or from a malignant transformation of a PA.[6] These two types usually show a different molecular pathway expression and immunohistochemical features.[6] The HER2 overexpression in SDC ranges from 15% to 44%.[14-17]

The management of SDC is complex and its prognosis remains poor.[5] Systemic chemotherapy shows a modest activity in patients with recurrent and/or metastatic SDC.[5] Several recent studies clearly demonstrated an improvement of the tumor control rate and the prognosis of the HER2-positive SDC by the addition of trastuzumab to chemotherapy.[18-27]

We report a case of a patient with a metastatic, HER2-positive parotid SDC efficiently treated with a weekly chemotherapy combined with a dual anti-HER2 treatment by trastuzumab and pertuzumab.

This is the first reported case showing an excellent activity of a such regimen in HER2-positive SDC.

2 | CASE REPORT

A 53-year-old, Caucasian, smoker man presented with a six-month history of a right facial neuralgia. He had concomitant noninsulin-dependent diabetes and a history of a Lyme disease that was treated by antibiotics in 2018. At the clinical examination, we found a hard, irregular, tumor lesion of the right parotid gland of 50 mm of diameter associated to a facial

paralysis. Biological tests were all in the normal ranges. The head and neck magnetic resonance imaging (MRI) revealed the presence of a necrotic tumor of 40 × 43 mm of the right parotid gland (Figure 1A, red arrows) with multiple, homolateral, cervical lymph nodes, a pathologic contrast uptake of the right facial nerve, the trigeminal ganglion and the internal auditory canal, a meningeal thickening of the right temporal convexity, and a multi-cystic metastasis of the right temporal lobe. The ^{18}F-FDG (^{18}F-fluorodeoxyglucose) PET scan documented an hypermetabolic, necrotic, tumor lesion of the right parotid (Figure 1B, red arrows), many hypermetabolic, homolateral, cervical lymph nodes, a brain metastasis of the right temporal lobe, and multiple bone metastases.

The patient referred to a percutaneous ultrasound-guided core biopsy of the parotid tumor. Histology revealed a massive infiltration of tumor cells with a large and pleomorphic nucleus and an abundant, eosinophilic cytoplasm, associated to a desmoplastic stroma reaction and a peri-nervous infiltration with no vascular invasion (Figure 1C). At the immunohistochemistry, tumor cells were positive for EMA, CK7, mammaglobin, androgen receptor (AR) and HER2 (Figure 1D) and negative for estrogens and progesterone receptor (ER, PR), PSA, S-100, actin, ACE, GATA-3, P40, p63, and CK-20. The translocation for the pleomorphic adenoma gene 1 (PLAG1) was positive according to the diagnosis of a SDC probably developed from a pre-existing pleomorphic adenoma (PA). Tumor cells did not harbor any neurotrophic receptor tyrosine kinase (NTRK) gene translocation. The proliferation index (Ki-67) was elevated at 50%.

Considering the tumor overexpression of the HER2 and the lack of the NTRK translocation, we started a systemic chemotherapy by a weekly carboplatin/paclitaxel regimen

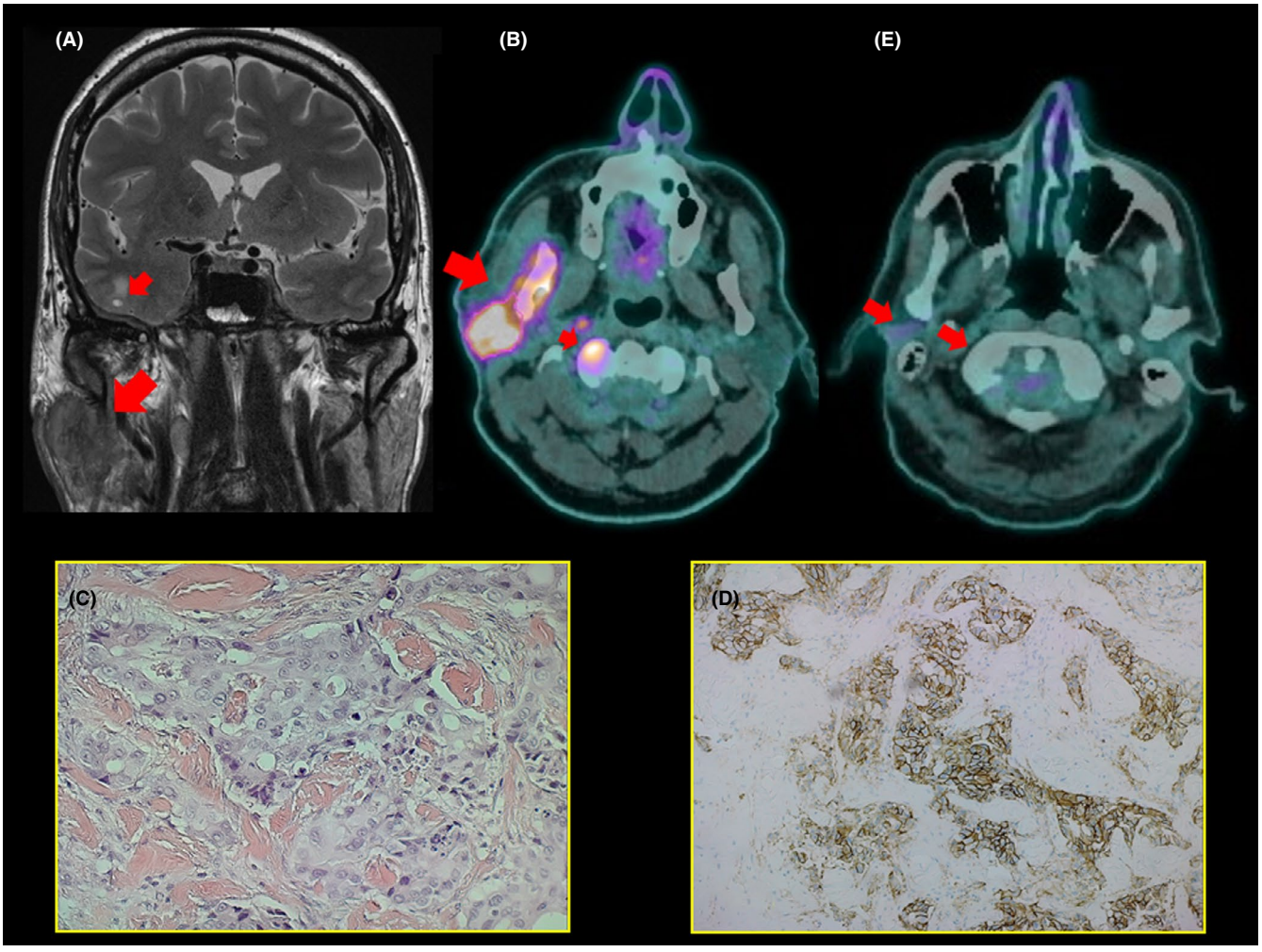

FIGURE 1 A, Necrotic tumor of the right parotid gland with a multi-cystic metastasis of the right temporal lobe (head and neck MRI: frontal section; red arrows). B, Hypermetabolic parotid tumor with a vertebral metastasis (PET scan; red arrows). C, Massive infiltration of tumor cells with a large and pleomorphic nucleus and an abundant, eosinophilic cytoplasm, associated to a desmoplastic stroma reaction and a peri-nervous infiltration with no vascular invasion (histology; hematoxylin and eosin stain, 200×). D, Diffuse and strong membranous staining for HER2 in tumor cells (immunohistochemistry; 200×). E, Major response to treatment of the primary parotid tumor and complete regression of the vertebral metastasis (PET scan; red arrows)

combined with trastuzumab and pertuzumab. After three months of treatment, the ^{18}F-FDG PET scan documented a complete regression of the brain metastasis and a partial response of the primary tumor, cervical lymph nodes, and bone metastases (Figure 1E, red arrows). Clinically, we observed an improvement of the right facial paralysis and neuralgia.

The patient is now alive, in good clinical conditions and always on chemotherapy. Three other cycles of treatment are programmed, followed by a trastuzumab/pertuzumab maintenance.

3 | DISCUSSION

Salivary duct carcinoma is an aggressive tumor that represents 1%-3% of all salivary gland malignancies [2]

Salivary duct carcinoma is often described in elderly patients and is frequently associated with a soft tissue extension and a perineural and lymphovascular invasion, which accounts for its high rate of local recurrence and distant metastasis.[2-4]

Several histological subtypes have been reported in the literature, including cribriform, papillary, solid, tubular, trabecular, single cells, and basal-like variants. Sarcomatoid, mucin-rich, micropapillary, and oncocytic variants are extremely rare.[2-4] Apocrine features, mainly eosinophilic cytoplasm and apical snouts, are usually described in SDC.[4] Immunohistochemically, SDC presents a typical expression of breast markers, such as gross cystic disease fluid protein-15 (GCDFP-15), mammaglobin, AR, β-catenin, CK5/6, p63, HER2, and GATA3; however, tumor overexpression of the ER-α and PR is rarely observed.[2-5]

Salivary duct carcinoma can develop de novo or from a malignant transformation of a PA.[6] The ex-PA SDC more commonly expresses epidermal growth factor receptor (EGFR), HER2, HER3, *TP53* mutations, high Ki-67, the high-mobility group AT-hook 2 (HMGA2), and PLAG1 [6] whereas de novo SDC frequently harbors *HRAS/PIK3CA* mutations but no *HER2* amplification.[6,7]

Many clinical and histological factors, including neck involvement, tumor size, older age, and the micropapillary and sarcomatoid variants, seem to be associated with a poor prognosis.[2-5] In a retrospective study, Jalaly *et al* demonstrated a strict correlation between the absence of the ER-ß overexpression and tumor aggressiveness.[8] However, the prognostic role of the other biomarkers remains controversial.[6,9]

Recently, based on a combination of ER, PR, HER2, EGFR, CK5/6, and Ki-67 status, two immunohistochemical classifications have been suggested, but their prognostic relevance has not be validated yet.[10,11] Di Palma et al reported a SDC classification into four subtypes: "luminal AR positive," "HER2 positive," "basal-like," and "intermediate".[12]

The determination of HER2 status plays a pivotal role in the SDC patients' selection and treatment.[13-17] The HER2 overexpression in SDC ranges from 15% to 44%.[14-17] In a recent study, using both immunohistochemistry and FISH analysis, this value was of 46%.[18] Additionally, a high concordance between HER2 3+ tumors and *HER2* amplification was found confirming the hypothesis of a correlation between the expression of HER2 protein and the *HER2* gene amplification. Therefore, the activation of the HER molecular pathway seems to be more important in the carcinogenesis of ex-PA than of de novo SDC.[18]

The management of SDC is complex and based on a multidisciplinary combined approach, including surgery and adjuvant radiotherapy.[5] Systemic chemotherapy, which is usually based on a combination of taxanes and platin salts, shows a modest activity in patients with recurrent and/or metastatic SDC.[3-5] The prognosis of SDC remains poor with only a few patients alive at 3 years from the diagnosis despite conventional therapy.[5]

As reported in recent published studies, the addition of the trastuzumab to chemotherapy improved the tumor control rate and the prognosis of the HER2-positive SDC.[19-27]

4 | CONCLUSION

In our case, the patient presented with a 6-month history of a right facial neuralgia and paralysis related to a metastatic, HER2-positive, parotid SDC.

This case highlights the rare entity, SDC, which is difficult to diagnose and manage. The diagnosis of the primary tumor was a challenge as the patient presented only with a trigeminal neuralgia. The facial paralysis appeared six months later. The ^{18}F-FDG PET and head and neck IRM showed a tumor lesion of the right parotid gland associated with an isolated brain metastasis and multiple, right, cervical lymph nodes and bone metastases. Histology and immunohistochemistry were consisted with the diagnosis of SDC. Considering the tumor HER2 overexpression, as for HER2-positive breast cancer, we started a systemic chemotherapy combined with trastuzumab and pertuzumab. This treatment was well tolerated, quickly improved the patient's symptoms, and allowed a major tumor, radiological response.

At our knowledge, it is the first published case of a metastatic, HER2-positive parotid SDC efficiently treated by a dual anti-HER2 treatment associated to a chemotherapy.

5 | CONSENT FOR PUBLICATION

A written informed consent was obtained from the patient for publication of this case report and any accompanying images. It is available for review by the *Editor-in-Chief* of the journal.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTIONS

The patient was admitted under the care and underwent systemic chemotherapy of RL. RL, MT, PL, MW, EAP, MC, FP, and AR substantially contributed to conception, acquisition, analysis, and interpretation of data. All authors have been involved in drafting, revising, and approving the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data and materials are available for review at the Division of Medical Oncology, CHR Metz-Thionville, in an electronic format.

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