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Case Report

Metastatic Salivary Duct Carcinoma with ERBB2 Amplification and Sequential Response to Ado-Trastuzumab Emtansine and Neratinib: A Case Report

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Keywords
ERBB2 · Salivary duct carcinoma · Neratinib · Electronically captured patient-reported outcomes · Case report

Abstract
Introduction: Salivary duct carcinoma (SDC) is an aggressive and rare subtype of salivary gland carcinoma. Surgical excision and radiotherapy are standard of care for early cancer. Chemotherapies with taxanes and platinum show overall response rates between 39% and 50%. SDCs are often associated with an overexpression of the androgen receptor (AR) and HER2/neu which have recently become druggable targets. ***Case Presentation:*** Here, we report on an 84-year-old male patient with metastatic SDC of the right parotid gland. In 2017, he underwent a right total parotidectomy, a right neck dissection, and an infratemporal fossa clearance followed by 6 weeks of radiotherapy. In 2018, due to metastatic spread in the lungs, bones, and pararenal gland, a pathological workup of the tumor tissue was performed and revealed both AR and HER2 overexpression, respectively. Consequently, he underwent androgen deprivation therapy and, due to asymptomatic progression, sequentially human epidermal growth factor receptor 2 (HER-2)-targeted therapy with ado-trastuzumab emtansine and neratinib, which led to stable disease during the course of about 18 months. The electronically captured patient-reported outcome had demonstrated a good tolerance of all three therapeutic lines. ***Conclusion:*** In conclusion, since effective standard therapeutic

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treatment options for SDC may often not be tolerable in older patients, the implementation of personalized and adaptive treatments, especially in patients with rare tumor types, might offer valuable treatment options.

Introduction

Salivary duct carcinomas (SDCs) are a rare (0.2–2% of all salivary gland tumors) and aggressive type of salivary gland carcinoma and are likely to form distant metastases [1, 2]. A review by Gilbert et al. [3] revealed that SDC is mainly diagnosed in elderly men, and in 83% of them, the tumor is located in the parotid gland. SDC frequently emerges from a pleomorphic adenoma which is speculated to be related to a worse disease-free survival but makes no difference in the overall survival when compared to de novo SDC [2, 3]. Standard treatment for early SDC includes surgical excision and radiation. Overall response rates for chemotherapy with taxanes and platinum in advanced cancer vary between 39% and 50% with a progression-free survival of about 8 months [2, 4]. More recently, in SDC, androgen receptor (AR) expression was reported; however, only a limited number of reports exist on treatment approaches related to this potential target [5]. Overexpression of human epidermal growth factor receptor 2 (HER-2), one of the four transmembrane tyrosine kinase receptors that are part of the human epidermal growth factor receptor family, may trigger cell proliferation and inhibition of apoptosis via dimerization of the extracellular domain through the RAS-MAP kinase and mTOR pathways [6]. Encouraging but fragmented studies and reports exist on the clinical benefit of HER-2-targeted treatments with and without chemotherapy [4]. The progression-free survival during androgen deprivation therapy varies between 4 and 9 months or even up to 23 months of stable disease depending on the combination of the hormone therapy, and in HER-2-targeted therapy, it varies between 9 and 32 months except for 1 patient who reached a complete response without progression at 53 months follow-up [4]. Here, we present an 84-year-old male patient with metastatic SDC of the right parotid gland, which demonstrated the overexpression of both AR and HER-2/neu (score 3; silver-enhanced in situ hybridization). Due to the patient's incapability to receive standard chemotherapy, alternative treatments were sequentially applied including AR blockade and the HER-2 targeting drugs ado-trastuzumab emtansine and neratinib.

Case Presentation

An 84-year-old male patient was diagnosed in 2017 at the age of 79 years with an SDC of the right parotid gland and right facial paresis, which indicates involvement of the facial nerve. The performed FDG-PET scan revealed a locally advanced disease with a 4-cm-measuring parotic tumor and involvement of numerous lymph nodes (8 of 31) on the right neck level I – III. He underwent a right total parotidectomy, a right neck dissection, and an infratemporal fossa clearance. The initial tumor stage was identified as T4a N2 M0. There was also description of lymphangiosis with extracapsular expansion and perineural invasion. Post-surgery, he subsequently underwent radiotherapy during 6 weeks. Eight months after the initial therapy, the patient developed several metastases in the lymph nodes, lungs, and bones. In June 2018, due to a lack of tolerable treatment

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options and an obvious strong nuclear expression of AR (>90% of tumor nuclei), he initiated treatment with the AR blocker bicalutamide (150 mg/day), combined with a luteinizing hormone-releasing hormone agonist monthly and a RANKL inhibitor every 6 weeks. Two months later, the patient underwent a follow-up FDG-PET scan, which demonstrated a first partial remission of all apparent metastases. In February 2019, a follow-up FDG-PET scan revealed a progression in size and high FDG activity of retrocaval lymph nodes, as well a progression of peribronchial metastases in the right lung, metastasis in the right adrenal gland, and a liver lesion in segment VII. After yet another CT scan in July 2019, progression of all metastatic lesions had significantly aggravated, indicated by novel bone metastases in the spine, retroperitoneal lymph node metastases, and pulmonary metastases. Hereafter, the patient initiated treatment with enzalutamide, a second-generation AR blocker with a higher affinity for AR when compared to bicalutamide [7]. With the intention to further detect potential characteristics for personalized therapies in the patient's tumor, an extensive pathological workup and immunohistochemistry of the tumor tissue was performed and revealed that the tumor was HER-2-positive for both the cell membrane and cytoplasm of tumor cells (IHC score 3; silver-enhanced in situ hybridization) yet PD-L1-negative as shown in Figure 1a–c. Next-generation sequencing (NGS, FoundationOne® CDx) had also been performed, which revealed that the AKT1 gene and the CDK6 gene were amplified. However, due to the limited availability of reliable treatments for these two genes, it was decided to target primarily the ERBB2 pathway as two recent studies had revealed an overall high response rate in patients with HER-2-amplified salivary gland carcinomas treated with ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate consisting of the monoclonal antibody trastuzumab linked to the microtubule poison DM1 [8]. Therefore, the patient initiated treatment with T-DM1, in August 2020. In October 2020, he underwent one more FDG-PET scan showing again a good partial metabolic response, which indicated that T-DM1 led to a robust partial remission as shown in Figure 2a–d (40% reduction of SUV max).

Due to an obvious progression in July 2021, we then initiated monotherapy with neratinib (240 mg/day), an irreversible tyrosine kinase inhibitor [9]. Clinical data on the efficacy of neratinib as a treatment of SDCs are described with clinical benefits of several months [8] and in patients suffering from SDC with brain metastases [10]. Although up to 85% of patients may suffer from diarrhea during treatment with neratinib, this compound was well tolerated by our patient, and he achieved good stable disease during this course of treatment [9]. Of note, during this treatment phase, the patient used the smartphone app medidux™ for standardized and structured reporting of treatment-related toxicities and well-being [11, 12], which also indicated that his quality of life was conserved and no dose limiting toxicities occurred (see example under TDM-1 therapy; shown in Fig. 3). During this observational period of almost 3 years and the sequential application of the abovementioned medications, no serious adverse events related to the drug intake were reported. For a comprehensive overview of drug intake and response, please refer to Table 1. Patient care was continuously provided by family members; no additional social support was required. During the course of treatment between June 2018 and November 2021, the patient maintained a robust well-being (average Karnofsky Index between 50 and 91) as well as a good cognitive and psychological state. No weight loss of more than 10% (CTCAE grade 1) occurred during the anti-HER2-directed treatment. In November 2021, we unfortunately lost track of our patient since he moved abroad.

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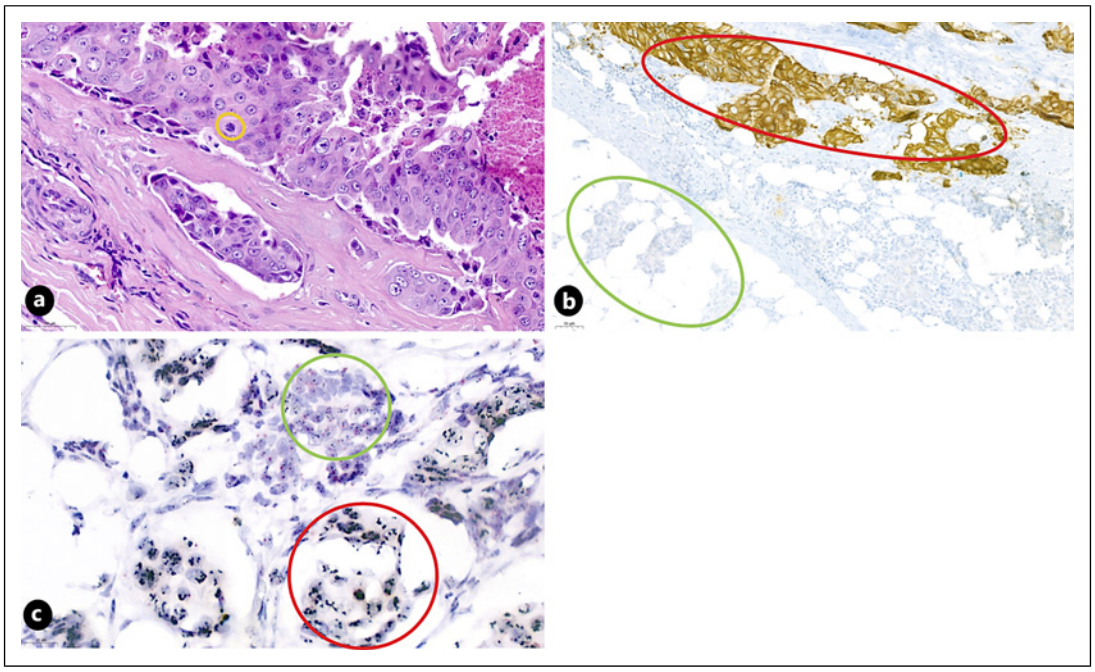

Fig. 1. Histology, immunohistochemistry, and silver-enhanced in situ hybridization (SISH) of the patient's tumor sample. **a** Tumor cells have a very typical large eosinophilic cytoplasm. The active mitosis (encircled) is further visible. **b** Immunohistochemistry for HER2 (clone 4B5, Ventana, Roche Diagnostics International, Rotkreuz, Switzerland): strong circular expression in most tumor cells (score 3+; brown) in comparison to negativity in the healthy parotid tissue (circle). **c** HER2-SISH (Ventana, HER2 Dual ISH DNA Probe, Roche Diagnostics International, Rotkreuz, Switzerland) with amplified HER2 gene status in tumor tissue (black signals, red circle) compared to healthy nuclei.

Discussion

Few reports exist on effective treatment options for elderly and frail patients suffering from metastatic SDC. Although treatment may seem successful at first in all subtypes of salivary gland carcinomas, advanced stages frequently relapse, and metastatic spread becomes a burden in an aging population [2]. With respect to demographics and tumor biology, an increasing number of reports on targeted treatments, in particular AR blockade and HER-2-targeted drugs such as T-DM1 and neratinib, can be found in the literature [4]. Disease control with both anti-hormonal strategies and growth factor receptor blockade demonstrates disease control comparable to conservative chemotherapeutic regimens, albeit with much lower collateral side effects [4–8]. However, as to our knowledge, a patient with sequential bicalutamide, enzalutamide, T-DM1, and neratinib therapy resulting in disease control of almost 3 years has not been reported previously. Since AR expression has been documented in the vast majority of tumors [8, 13], and HER-2 overexpression in SDC is prevalent in up to 50%, the exploration of already available and novel compounds, including antibody-drug conjugates, is warranted. HER2-targeted therapies have entered into the clinical practice of a plethora of solid tumors including breast, ovarian, gastric, esophageal, endometrial, lung, bladder, and oropharynx. Prospective registries might evaluate how far relatively innovative drugs can also overcome potential HER2 resistances and improve the patient outcome [14–17]. Indicatively, one recent case report documented a complete response to fam-trastuzumab deruxtecan after disease progression on neratinib and T-DM1 [8]. We also observed the importance and relevance of personalized and adaptive treatments,

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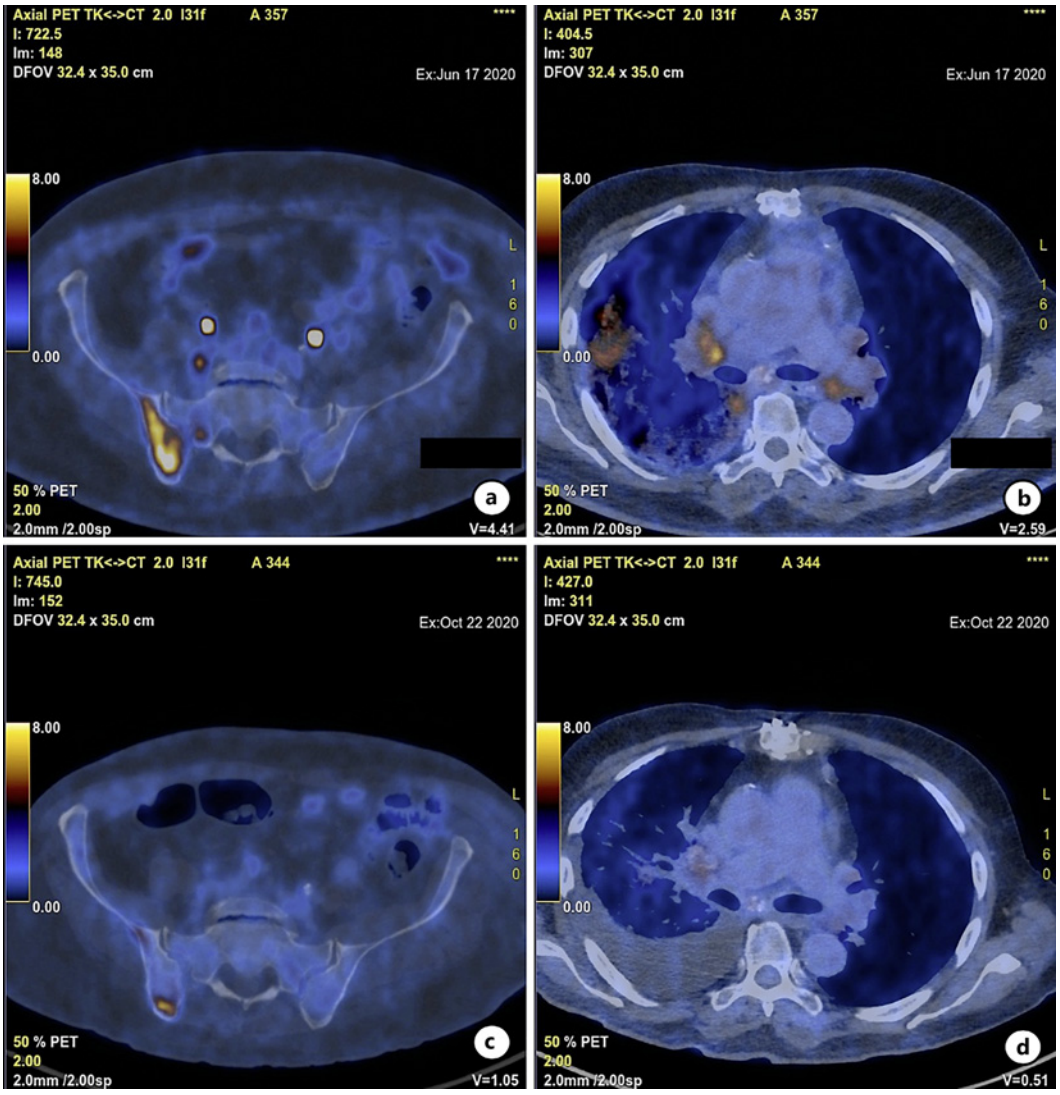

Fig. 2. a CT scan of the pelvic region showing a clearly in size progressive intraosseous metastasis in the right posterior superior iliac spine before T-DM1 treatment. **b** CT scan of the lung showing several metastases in the right and left lung. **c** CT scan of the pelvic region 2 months after the initiation of T-DM1 treatment. **d** CT scan of the lung 2 months after the initiation of T-DM1 treatment, demonstrating a robust partial remission. There is a moderate pleural infusion and atelectasis visible in the right lung.

especially in patients with rare tumors, like SDC, according to the tumor's biology and stress the significance of exploring treatment options and reimbursement streams progressively based also on real-world well-being and performance as is reported by the patient (electronically captured patient-reported outcomes) [12]. This approach is likely to assist in the conduct of clinical trials and registries by gathering treatment-related information on potential toxicities and outcomes from empowered patients in less time and with less expense. In addition, physician-doctor symptom review and instructions on potential self-effective measures can reassure patients in situations where medication might be on off-label use and stimulate adherence and save use when dealing with these medications, resulting in long-term efficacy. To our knowledge, this is the first report describing a patient with metastatic SDC who received AR blockade with bicalutamide, enzalutamide, and sequentially applied

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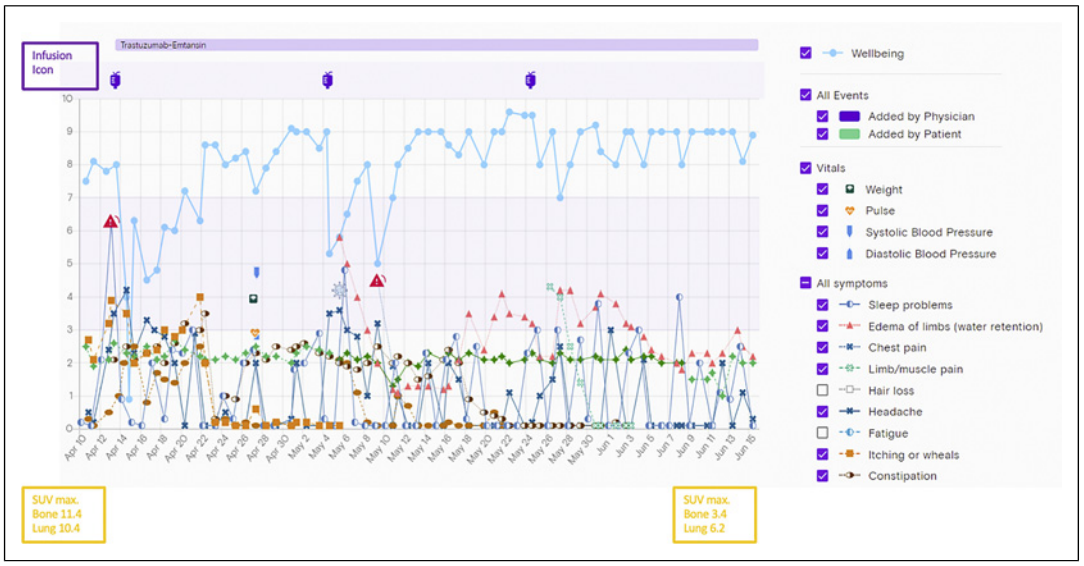

Fig. 3. Graphic of ePROs reported from the patient during his treatment with T-DM1. Drug-induced timing and correlation to tumor size according to SUVmax (PET scan) are indicated in violet and yellow. Light blue, well-being; blue circle, sleep problems; red, edema of limbs; mint green, limb/muscle pain; blue x, headache; orange, itching or wheals; brown, constipation. ePROs, electronically captured patient-reported outcomes.

Table 1. Overview of applied medication and best response

Medication	Application period	Best response
Bicalutamide/Zoladex	June 2018–July 2019	Partial remission
Enzalutamide/Zoladex	July 2019–July 2020	Partial remission
T-DM1	August 2020–July 2021	Partial remission
Neratinib	July 2021–November 2021	Stable disease

HER-2-targeted therapy with TDM1 and neratinib with almost 3 years of disease control. Lastly, the CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535097).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Conflict of Interest Statement

A.T. is an initiator and stock owner of mobile Health AG, a startup company that operates the Medidux Smartphone App. He serves as a chief medical officer for the startup company. Y.K. is the commercial project manager and customer success manager of mobile Health AG.

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Author Contributions

The authors A.T., T.F.H., S.P.S., and M.T. are physicians and contributed to the design and conduct of the study and on writing the manuscript. N.A. is a medical student. Y.K. is an economist and former medical student. A.T. and N.A. wrote the manuscript. Final approval of the manuscript was provided by all the authors. A.T. is the guarantor of integrity of the entire study. A.T., T.F.H., S.P.S., and M.T. contributed to study concepts and design. A.T. and N.A. contributed to literature research. A.T. contributed to clinical studies. A.T, S.P.S., and M.T. contributed to experimental studies/data analysis. N.A. contributed to statistical analyses. N.A., A.T., and Y.K. contributed to manuscript preparation. Y.K., K.S.R., and M.T. participated in manuscript editing.

Data Availability Statement

Data were available from medical records and the medical device patient app. All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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