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Case Report

Androgen Deprivation Therapy for Intracranial Metastasis of a Salivary Duct Carcinoma: Case Report

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Salivary duct carcinoma · Androgen deprivation · Intracranial metastasis · Case report

Abstract
Salivary duct carcinoma (SDC) is a rare subtype of salivary cancers associated with androgen receptor and human epidermal growth factor receptor 2 (HER2/neu) overexpression. It shows a high propensity to give rise to distant metastases mainly to the lung, the bone, and the liver. Intracranial metastases are rare. We report the case of a 61-year-old male patient with SDC developing intracranial metastases. Unresponsive to radiotherapy and anti-HER/neu targeted therapy the intracranial metastases showed a very good partial remission to androgen deprivation therapy with goserelin acetate. This case demonstrates the potential of a highly targeted therapy with a relatively cheap and well-known drug in a patient with a rare disease without other good therapeutic options, which is a good example of modern, personalized medicine.

Introduction

Salivary duct carcinoma (SDC) is an aggressive and rare type of primary salivary gland cancer (SGC) with a high potential for distant metastases. It was first described by Kleinsasser et al. [1] and accounts for up to 2% of all primary salivary epithelial neoplasms [2]. The incidence of SGC is low with only 0.6–1 per 100,000 persons [3]. The majority of SGCs are found in the parotid gland (70% of cases), but they also arise in the submandibular gland (20–25%) or in minor salivary glands (5–10%) that populate the upper aerodigestive tract

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[3]. Most cases develop de novo, although some may represent the malignant component of carcinoma ex pleomorphic adenoma [2]. The World Health Organization classifies 24 subtypes of SGC, which show significant variation in histological and clinical features [4]. Histologically, SDC resembles ductal carcinoma of the breast and is characterized by an abundant eosinophilic granular cytoplasm and pleomorphic nuclei with prominent nucleoli and intraductal comedo necrosis [5]. Metastases to the lung, the bone, and the liver are most common; however, intracranial metastases are very rare [4]. Boon et al. [6] reported 177 patients diagnosed with SDC between 1990 and 2014. Brain metastases occurred in 15 (18%) of them. Another retrospective analysis of 141 patients with SDC revealed that only 3 patients (2.1%) developed brain metastases [7]. We report a male patient with intracranial metastases of an SDC treated successfully with androgen deprivation therapy (ADT). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529470).

Case Presentation

A 61-year-old male patient presented in August 2017 with hoarseness due to a motility disorder of the vocal cords. A PET-CT-scan showed a tumor in the left upper lobe of the lung involving the left laryngeal nerve, several pulmonary metastases, metastasis-suspicious mediastinal lymph nodes, and several osteolytic lesions throughout the axial skeleton, most likely compatible with a non-small cell lung cancer. Histological analyses showed a non-small cell carcinoma. Due to hearing loss, an MRI of the neurocranium was performed which showed in addition a tumor in the pontocerebellar angle compatible with a meningioma.

In 2013, he underwent resection of a tumor of the right sided glandula submandibularis which was histologically described as an acinic cell carcinoma, along with neck dissection followed by adjuvant cisplatin-based radio-chemotherapy. The histological comparison of the lung tumor with the salivary gland tumor from 2013 showed consistent findings. Further immunohistochemical studies showed positivity for androgen receptor and HER2/neu (2+ positive, but no HER2 amplification), in both tumors, as described for SDC. In retrospect, it can be assumed that the tumor in 2013 was an SDC, which has now relapsed with multiple metastases, rather than acinic cell carcinoma, since it did not show expression of DOG1, SOX10, or amylase (Fig. 1a + b).

Palliative chemotherapy for metastatic disease with cisplatin and pemetrexed was initiated and resulted in a partial remission of the lung and lymph node metastases. The tumor in the pontocerebellar angle was also regressive, so that it was then considered to be a brain metastasis of the SDC, rather than meningioma. After a few months, the patient's hearing deteriorated and an MRI scan of the head showed progressive growth of the tumor in the cerebellopontine angle with almost complete obliteration of the auditory canal. In parallel, the lung and bone metastases were also progressive. Radiotherapy of the intracranial lesion with 39 Gy (IMRT) was performed resulting in a locally stable situation. Immunotherapy with the checkpoint inhibitor nivolumab over 6 months did not show any response. A reuptake of chemotherapy with platin and pemetrexed in January 2019 resulted again in a partial remission, followed by a clinically stable situation for almost 1 year.

In January 2020, blurred vision led to an ophthalmologic exam which revealed a retinal metastasis. An MRI of the neurocranium showed progressive intracranial metastases with increasing infiltration of the internal acoustic meatus and increasing extension to the clivus. In addition, there was an infiltration along the facial and vestibulocochlear nerves on the left, up to the brainstem. The mediastinal and hilar metastases were also progressive. Stereotactic radiotherapy to the retina with 44 Gy was applied. Based on the immunohistochemical

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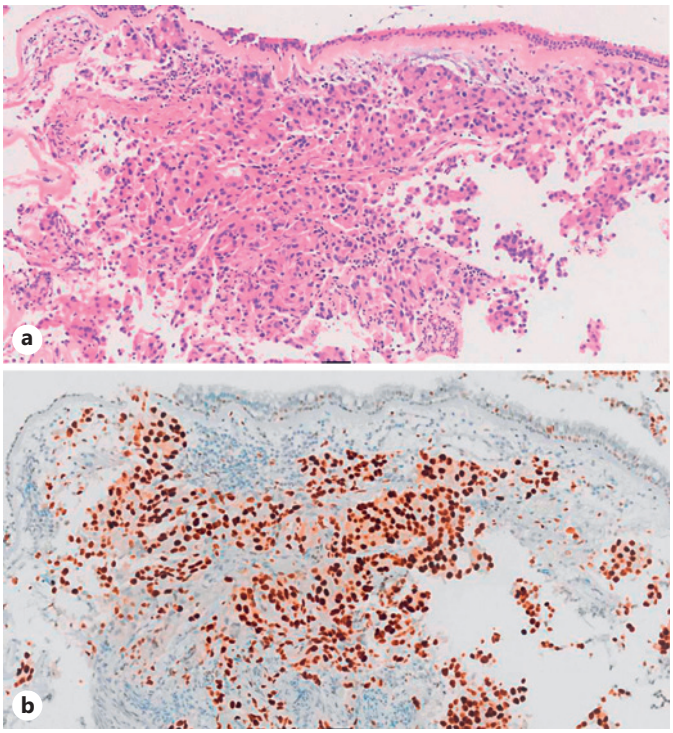

Fig. 1. a Bronchial biopsy with metastasis of the salivary duct carcinoma: HE. **b** Nuclear androgen receptor immunoexpression (original magnification, ×100).

positivity for HER2/neu, treatment with trastuzumab was initiated. However, after 6 months of trastuzumab, the intracranial, lymphatic, adrenal, and pulmonary metastases were progressive. In addition, new muscle and soft tissue metastases were found. The pulmonary metastasis led to coughing and pretracheal lymph node metastases led to a progressive and clinically relevant stenosis of the superior vena cava. In September 2020, ADT with goserelin acetate 10.8 µg every 3 months was initiated (together with bicalutamide over 2 weeks for bicalutamide flare prevention). ADT was well tolerated with minimal hot flushes. After a few weeks, a clear clinical benefit with disappearance of the cough and improvement of the dyspnea could be observed. The CT scan of the lung 6 months after start of ADT showed a very good partial remission (PR) (Fig. 2a + b), and the MRI of the neurocranium showed a regression of the intracranial metastases (Fig. 3a + b). Since then, the situation has been clinically and radiologically stable and the MRI of the head from November 2021, 14 months after initiation of ADT continues to show regression of the intracranial tumor manifestations. A timeline of the main therapies and responses is given in Figure 4.

Discussion

Intracranial metastases in SDC are very rare. As in our patient, intracranial metastases typically present 3–7 years after treatment of the primary tumor [4]. The standard treatment consists of surgery and radiation therapy. In the event of treatment failure or recurrence, systemic therapy is required. However, there are little data on the treatment of metastatic SDC, particularly in brain metastases. In analogy to other tumor entities, primary chemotherapy and/or targeted therapy is frequently applied. Histologically, SDC resembles ductal breast cancer and shows frequently immunohistochemical positivity for HER2/neu (25–90%). In

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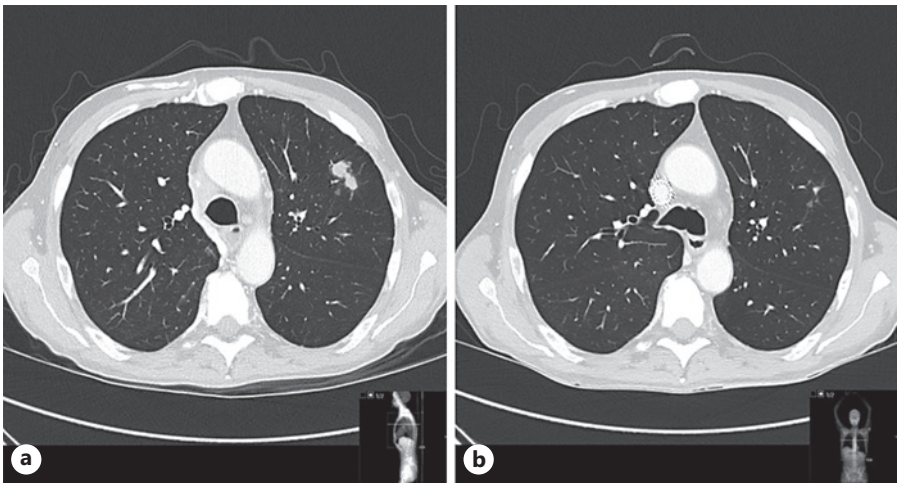

Fig. 2. Thorax CT-scan axial/transversal before (09/2020, **a**) and after treatment (04/2021, **b**).

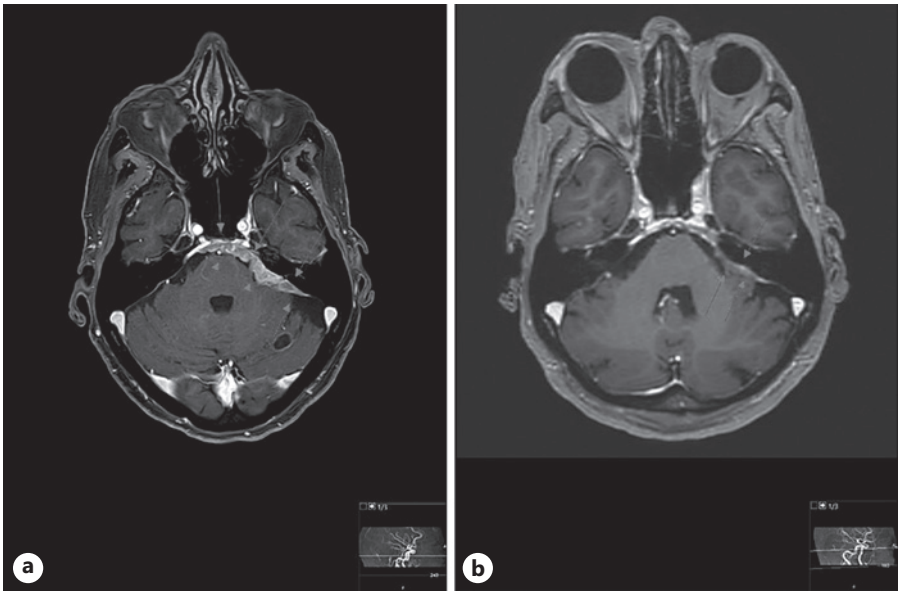

Fig. 3. MRI of the neurocranium T1-spin echo-sequence with contrast medium. Extra-axial mass at the left cerebellar pontine angle before (08/2020, **a**) and after treatment (11/2021, **b**).

addition, expression of the androgen receptor is a common feature of the SDC (67–83%). In contrast to ductal breast cancer, however, positivity for estrogen receptors (1.3%) or progesterone receptors is a rarity [2, 8, 9].

Targeted therapies with HER2/neu inhibition and ADT have resulted in objective responses as single agents or in combination with chemotherapy [10, 11]. However, there are no data regarding the optimal targets, the sequence, and a possible combination of these therapies.

After failure of chemotherapy and immunotherapy, we decided to start treatment with trastuzumab. It remains unclear whether the immunohistochemical detection of HER2/neu represents a sufficiently reliable, predictive biomarker. In some studies which defined HER2/neu positivity by fluorescence in situ hybridization amplification HER2/neu positivity was

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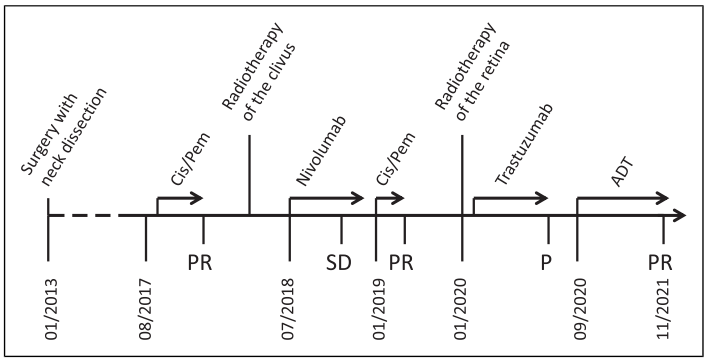

Fig. 4. Timeline of the main therapies and responses. P, progressive disease; PR, partial remission; SD, stable disease; Cis/Pem, chemotherapy with cisplatin and pemetrexed; ADT, androgen deprivation therapy.

found in only 15–40% [2, 12]. However, after 6 months of treatment, there was a progression in almost all localizations, especially the brain metastases.

After the onset of androgen deprivation, we observed a partial response with regression of both the intracranial and the other distant metastases. The intracranial metastases were histologically not proven, but rapid progression and an excellent response to therapy supported the thesis that the intracranial lesions were also metastases of the SDC, rather than meningioma. Meningioma expressing hormonal receptors exist [13]. However, it is highly unlikely that there is a response of histologically proven lung metastases to androgen deprivation and independently a response of a meningioma to the same hormonal maneuver.

The activity of ADT in AR-positive SDC has already been shown in several small retrospective studies. Remission rates between 50% [14] and 88% [15] had been shown. The median progression-free survival in responsive patients ranged from 12 to 14.8 months. One of the biggest retrospective analyses with 86 patients, 35 of whom were treated with ADT, in Netherlands showed a partial remission in 18% cases, stable disease in 32% cases, leading to a clinical benefit ratio of 50%. The median OS was 17 months versus 5 months in 43 patients receiving best supportive care [11]. At the moment, it is unclear whether chemotherapy or ADT is the more effective therapy. To this aim, there is an ongoing European Organization for Research and Treatment of Cancer (EORTC) prospective trial to evaluate the efficacy and safety of chemotherapy versus ADT in patients with recurrent and/or metastatic AR expressing SGCs (NCT01969578). In AR-expressing castration-resistant SGCs, the activity of abiraterone will be tested (NCT02867852). We think that AR-directed therapies by testosterone deprivation (surgical castration, LH-RH agonists and antagonist and abiraterone) and androgen receptor inhibition, e.g., with bicalutamide, enzalutamide, or apalutamide might become a mainstay of treatment in AR-positive SDCs over the next few years.

Conclusion

We report a case of a male with metastatic SDC with partial remission under ADT after progression with chemotherapy, radiation, and targeted therapy with trastuzumab. To our knowledge, this is the first case of a patient with intracranial metastases of SDC responding to ADT. ADT is a relatively cheap and highly targeted therapy and therefore a good example of modern personalized medicine.

Statement of Ethics

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

Conflict of Interest Statement

The authors declare to have no conflict of interest related to this work.

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Author Contributions

Manuel Rösch and Martin Buess: designed the case report; Spasenija Savic Prince: provided and interpreted the histology analysis; Christian Bieg: provided and interpreted CT and MRI scans; Manuel Rösch and Martin Buess: wrote the manuscript; all authors revised and approved the final manuscript and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data that support the findings of this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Kleinsasser O, Klein HJ, Hübner G. [Salivary duct carcinoma. A group of salivary gland tumors analogous to mammary duct carcinoma]. Arch Klin Exp Ohren Nasen Kehlkopfheilkd. 1968;192(1):100–5.
2 Simpson RHW. Salivary duct carcinoma: new developments--morphological variants including pure in situ high grade lesions; proposed molecular classification. Head Neck Pathol. 2013;7(Suppl 1):S48–58.
3 D'heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. Curr Opin Otolaryngol Head Neck Surg. 2018;26(2):142–51.
4 Venteicher AS, Walcott BP, Sheth SA, Snuderl M, Patel AP, Curry WT, et al. Clinical features of brain metastasis from salivary gland tumors. J Clin Neurosci. 2013;20(11):1533–7.
5 Williams L, Thompson LDR, Seethala RR, Weinreb I, Assaad AM, Tuluc M, et al. Salivary duct carcinoma: the predominance of apocrine morphology, prevalence of histologic variants, and androgen receptor expression. Am J Surg Pathol. 2015;39(5):705–13.
6 Boon E, Bel M, van der Graaf WT, van Es RJJ, Eerenstein S, Baatenburg De Jong R, et al. Salivary duct carcinoma: clinical outcomes and prognostic factors in 157 patients and results of androgen deprivation therapy in recurrent disease (*N* = 31)—study of the Dutch head and neck society (DHNS). JCO. 2016;34(15_Suppl l):6016.
7 Otsuka K, Imanishi Y, Habu N, Sato Y, Shigetomi S, Fujii R, et al. [Survival analysis and immunohistochemical study of HER-2 and AR (androgen receptor) expression in salivary duct carcinoma]. Nippon Jibiinkoka Gakkai Kaiho. 2013;116(9):1024–32.
8 Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. Mod Pathol. 1998;11:1033–8.

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DOI: 10.1159/000529470

9 Simpson RHW, Skálová A, Di Palma S, Leivo I. Recent advances in the diagnostic pathology of salivary carcinomas. Virchows Arch. 2014;465(4):371–84.
10 Alotaibi AM, Alqarni MA, Alnobi A, Tarakji B. Human epidermal growth factor receptor 2 (HER2/Neu) in salivary gland carcinomas: a review of literature. J Clin Diagn Res. 2015;9:ZE04–08.
11 Boon E, van Boxtel W, Buter J, Baatenburg de Jong RJ, van Es RJJ, Bel M, et al. Androgen deprivation therapy for androgen receptor-positive advanced salivary duct carcinoma: a nationwide case series of 35 patients in The Netherlands. Head Neck. 2018;40(3):605–13.
12 Williams MD, Roberts DB, Kies MS, Mao L, Weber RS, El-Naggar AK. Genetic and expression analysis of HER-2 and EGFR genes in salivary duct carcinoma: empirical and therapeutic significance. Clin Cancer Res. 2010;16(8):2266–74.
13 Smith DA, Cahill DW. The biology of meningiomas. Neurosurg Clin N Am. 1994;5(2):201–15.
14 Locati LD, Perrone F, Cortelazzi B, Lo Vullo S, Bossi P, Dagrada G, et al. Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed androgen receptor-positive salivary gland cancers. Head Neck. 2016;38(5):724–31.
15 Jaspers HCJ, Verbist BM, Schoffelen R, Mattijssen V, Slootweg PJ, van der Graaf WTA, et al. Androgen receptor-positive salivary duct carcinoma: a disease entity with promising new treatment options. J Clin Oncol. 2011;29(16):e473–6.