LETTER TO THE EDITOR

# Salivary gland carcinomas with unusual presentations

Carl Frederik Haugaard[a], Tina Klitmøller Agander[b], Giedrius Lelkaitis[b], Kim Francis Andersen[c], Simon Andreasen[a,b] and Irene Wessel[a]

[a]Department of Otorhinolaryngology Head & Neck Surgery and Audiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [c]Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

## Introduction

Carcinomas of the salivary glands constitute a large and heterogeneous group of lesions [1]. In addition to their distinctive morphology, different types of salivary gland carcinoma have marked differences in clinical behavior, especially with respect to metastatic potential.

Carcinoma ex-pleomorphic adenoma (CA-ex-PA) is defined as a carcinoma arising from a pleomorphic adenoma (PA), with the malignant component most often being a high-grade adenocarcinoma but can be any carcinoma type [1]. CA-ex-PA is divided into intracapsular, minimally invasive (<4 mm), and widely invasive (>4 mm) lesions, with the former being without malignant potential and the latter being a high-grade lesion with up to 70% developing distant metastasis [1]. The clinical presentation of the CA-ex-PA is usually rapid growth in a longstanding salivary gland mass, typically in older adults [2]. Sarcomatoid salivary duct carcinoma (SDC) is a relatively new and rare tumor subtype originally described as a composite of SDC and sarcomatoid carcinoma in a case series with three patients, of which none had rhabdoid features (SDCRF) [3]. In 2004, a case series of eight sarcomatoid SDCs reported only one with rhabdoid features, supporting this as a new tumor subtype of sarcomatoid SDC [4]. Recently, the largest material so far was published, including nine SDCRFs patients [5]. So far, the clinical relevance of this tumor subtype is not known.

Despite the well-known metastatic potential of various types of salivary gland carcinoma, cases presenting with metastatic disease usually present with a concomitant salivary gland mass giving hint to the primary tumor origin. To our knowledge, no reports of CA-ex-PA presenting only with lumbar pain or SDC presenting only with syncope as the initial symptoms have been published.

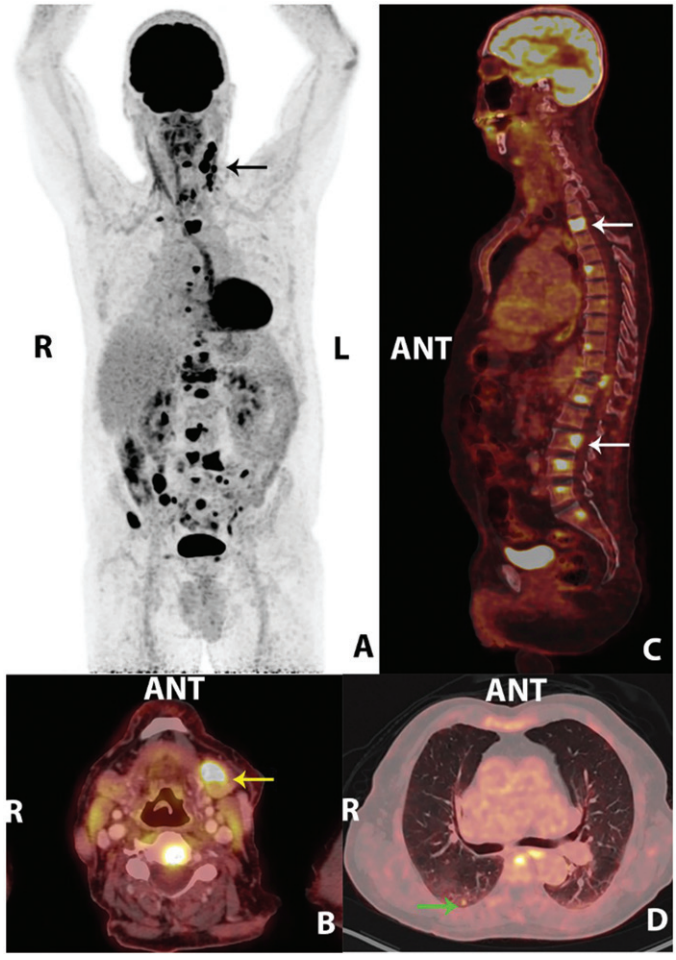


**Figure 1.** Case 1: baseline $^{18}$F-FDG PET/CT. PET maximal intensity projection (A) and fused PET/CT (B–D) images demonstrate extensive metabolically active metastatic disease, suggesting the primary tumor to be in the left submandibular gland (B, yellow arrow), with multiple metastatic ipsilateral lymph nodes on the neck (A, black arrow), a right-sided lung metastasis (D, green arrow), and multiple metastases in the axial skeleton (C, white arrows).

## Case 1

A 70-year-old male with no previous medical history presented with midline lumbar pain. Spinal X-ray revealed a collapsed vertebra on the level of TH12 and magnetic resonance imaging (MRI) revealed multiple lytic metastases of the spine and sacrum. Computed tomography (CT) scan of the abdomen and thorax was performed without identification of a primary malignancy. Full-body fluorine-18 labeled

CONTACT Carl Frederik Haugaard cfhaugaard@gmail.com Department of Otorhinolaryngology Head & Neck Surgery and Audiology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København Ø, Copenhagen, Denmark

Supplemental data for this article can be accessed here.



https://doi.org/10.1080/0284186X.2019.1566768

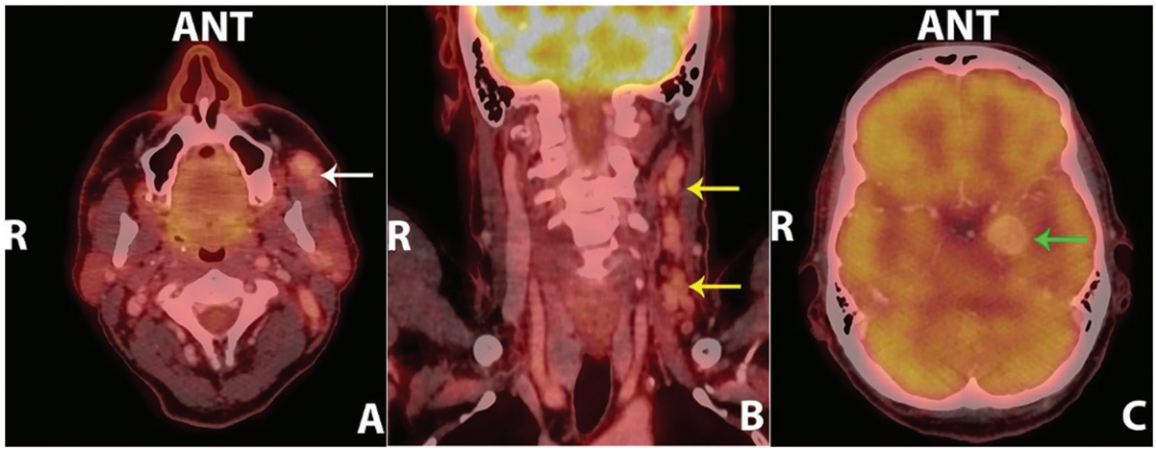


**Figure 2.** Case 2: baseline $^{18}$F-FDG PET/CT. Fused PET/CT images (A–C) demonstrate the primary tumor in the left masseter muscle (A, white arrow), multiple metastatic lymph nodes ipsilaterally on the neck (B, yellow arrows) and brain metastases (C, green arrow). All lesions with relatively low metabolic activity.

fluoro-deoxy-glucose ($^{18}$F-FDG) positron emission tomography (PET)-CT scan showed extensive metabolically active metastatic disease, a tumor in the left submandibular gland, multiple metastatic ipsilateral lymph nodes on the neck, a right-sided lung metastasis, and multiple metastases in the axial skeleton (Figure 1). Ultrasonography revealed an inhomogeneous tumor in the left submandibular gland measuring 2.1 × 1.6 × 2.0 cm and multiple pathological ipsilateral lymph nodes. For diagnostic purposes, the patient underwent surgical excision of the submandibular mass and the two cervical lymph nodes, and CT-guided biopsy was performed of an iliac lesion.

Histopathology showed a partially encapsulated tumor with a central part constituted by an almost completely hyalinized PA measuring 8 mm in diameter with transition to an SDC invading 14 mm into the surrounding parenchyma (supplementary Figure 1). By immunohistochemistry, the malignant tumor cells were positive for epithelial membrane antigen (EMA), cytokeratin 7 (CK7) and human epidermal growth factor receptor 2 (HER2) (supplementary Figure 1). Androgen receptor (AR) was positive in 30% of tumor cells. Proliferation index was 40% as estimated with Ki-67. Thyroid transcription factor-1 (TTF-1), prostate-specific antigen (PSA) and gastrointestinal markers were negative. Vascular and neural invasion was evident, and the surgical margins were involved. Biopsies from os ilium showed coherent groups of epithelial cells with large nuclei and amphophilic cytoplasm with some vesicles. The epithelial cells were CK7, and EMA positive and overexpressed HER2 while cytokeratin 20 (CK20), caudal type homeobox factor 2 (Cdx2), PSA and TTF-1 were negative, compatible with metastasis from CA-ex-PA.

Palliative radiotherapy directed at the primary tumor and neck, 3 Gy × 10, and the spinal metastasis, 5 Gy × 5 was performed. A follow-up $^{18}$F-FDG PET-CT scan was performed 2½ months after ended radiotherapy showed multiple new lung metastases and progression of the bony metastases. As the patient's tumor was HER-2 positive, the patient was referred for experimental treatment with trastuzumab and paclitaxel and received further palliative radiotherapy directed at the spinal metastasis, 5 Gy × 5. After eight series of trastuzumab and paclitaxel, no progression of the metastasis was noted. The patient was still alive 12 months after diagnosis.

## Case 2

A 56-year-old male with no previous medical history was admitted to the emergency ward due to syncope and presyncope during the last two days. MRI scan of the cerebrum showed approximately 20, contrast-enhancing tumors in both cerebral hemispheres. CT-scan of neck, thorax and abdomen demonstrated a mass in the left masseter muscle and multiple enlarged ipsilateral small lymph nodes. Ultrasonography showed a 2 × 2 × 1 cm hypoechoic process in the masseter muscle without extra parenchymal growth and several enlarged (>1 cm), round and hypoechoic lymph nodes in level II-IV. $^{18}$F-FDG PET-CT scan showed low metabolic activity of all lesions (Figure 2). FNA was uninformative, and a cervical lymph node was excised for diagnosis. Histopathology of the lymph node showed metastatic tumor cells positive for AR, GATA-3, HER2 and gross cystic disease fluid protein-15 (GCDFP-15), thus increasing the probability of salivary gland carcinoma. As a diagnostic measure, the tumor of the masseter muscle was removed.

Histopathology showed a diffusely infiltrating tumor with involved margins without residual PA. Centrally, several larger blood vessels had tumor emboli (supplementary Figure 2). Tumor cells were positive for CK7, HER2, GATA3, GCDFP-15, epidermal growth factor receptor (EGFR), p53 and AR. Some tumor cells were positive for mammaglobin, whereas all cells were negative for vimentin and negative or weakly positive for E-cadherin (supplementary Figure 2). The proliferation index, labeled with Ki-67, was 60%.

Biopsies of the brain lesions as further diagnostics was not performed as it would not change the treatment regime, compared with the risk imposed on the patient. The final diagnosis was henceforth SDC T1N2aM1 with rhabdoid features. Concluding treatment was palliative radiation therapy toward the cerebrum, 3 Gy × 10 and palliative radiotherapy

toward the primary tumor and neck, 4 Gy × 13. As progression with medullary metastasis was noticed and the tumor was strongly AR positive, palliative radiotherapy toward the medulla, 5 Gy × 5, and bicalutamide treatment was initiated. The patient discontinued the use of bicalutamide after 10 days due to side effects. The patient died 11 months after diagnosis.

## Discussion

The two present cases demonstrate the heterogeneity of the clinical presentation of salivary gland tumors and the challenges in the diagnostic work-up imposed by this. In case 1, the primary salivary gland carcinoma was not recognized until full body $^{18}$F-FDG PET-CT was employed. The rarity of salivary gland primary tumors in skeletal metastases of unknown origin is illustrated by The Scandinavian Sarcoma Group Skeletal Metastasis Registry, which is the largest registry of surgically treated skeletal metastases in the world, which found that in 1107 patients, only 22 metastases came from the head and neck area (13 thyroid, five larynx and four tongue) [6]. Furthermore, for a male in the 7th or 8th decade, the most probable primary tumor location would be prostate, lung and bladder in that order [6]. The primary tumor was relatively small; hence no swelling of the neck was noticed. Still, the patient had disseminated disease stressing the importance of the level of invasiveness and not tumor size in CA-ex-PA. As the disease was disseminated, the patient was technically inoperable. This warrants radiotherapy as main therapy as shown previously [7–9]. HER2-directed therapy has been tested in small series with some effect [10–12]. The stabilization of disease in this case supports a role for HER2-directed therapy in HER2-positive SDC.

Case 2 was a histologically very rare variant of SDC, SDCRF. Recently, the largest material so far was published, including nine SDCRF patients [5]. In this material, it is discussed that SDCRF does not show histologically sarcomatoid traits, e.g., not being positive for vimentin. Furthermore, SDCRF showed positivity for AR and GCDFP-15 and in some cases HER2 positivity as well as features of SDC. Hence the argument was that SDCRF was a separate SDC subtype and not a subtype of sarcomatoid SDC. Our case shows typical immunohistochemical profile of SDCRF with positive reaction for CK7, GCDFP-15, AR, and overexpression of HER2, as well as negative/weak reaction for E-cadherin and negative reaction for vimentin. With the information available in the relative few cases reported, our case supports the notion that SDCRF is a unique subtype of SDC rather than a variant of sarcomatoid SDC. The clinical relevance of this tumor subtype has not yet been determined as this is a relatively new and rare tumor subtype.

In conclusion, salivary gland carcinomas can present in multiple ways with lumbar pain or syncope being two unusual variants. The heterogeneity and aggressiveness of salivary gland carcinomas must also be kept in mind even when dealing with small tumors. Furthermore, a patient with synchronous SDC and bone metastasis at the time of diagnosis should always have a biopsy of the latter as the probability of another synchronous cancer, especially in the later decades of life, is high. Our case also supports the view of SDCRF as a separate SDC subtype rather than a variant of sarcomatoid SDC.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## ORCID

Carl Frederik Haugaard http://orcid.org/0000-0002-9947-8703
Simon Andreasen http://orcid.org/0000-0002-1528-4988
Irene Wessel http://orcid.org/0000-0001-9986-5001

## References

[1] El-Naggar AK, Chan JKC, Grandis JR, et al. WHO classification of head and neck tumours. Lyon: International Agency for Research on Cancer; 2017.
[2] Andreasen S, Therkildsen MH, Bjørndal K, et al. Pleomorphic adenoma of the parotid gland 1985–2010: a Danish nationwide study of incidence, recurrence rate, and malignant transformation. Head Neck. 2016;38:E1364–E1369.
[3] Henley JD, Seo IS, Dayan D, et al. Sarcomatoid salivary duct carcinoma of the parotid gland. Hum Pathol. 2000;31:208–213.
[4] Nagao T, Gaffey TA, Serizawa H, et al. Sarcomatoid variant of salivary duct carcinoma. Am J Clin Pathol. 2004;122:222–231.
[5] Kusafuka K, Kawasaki T, Maeda M, et al. Salivary duct carcinoma with rhabdoid features: a salivary counterpart of pleomorphic lobular carcinoma of the breast. Histopathology. 2017;70:164–173.
[6] Ratasvuori M, Wedin R, Keller J, et al. Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg Oncol. 2013;22:132–138.
[7] Chen AM, Bucci MK, Quivey JM, et al. Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. Int J Radiat Oncol. 2006;66:1044–1050.
[8] Mendenhall WM, Morris CG, Amdur RJ, et al. Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer. 2005;103:2544–2550.
[9] Terhaard CHJ, Lubsen H, Rasch CRN, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol. 2005;61:103–111.
[10] Thorpe LM, Schrock AB, Erlich RL, et al. Significant and durable clinical benefit from trastuzumab in 2 patients with HER2-amplified salivary gland cancer and a review of the literature. Head Neck. 2017;39:E40–E44.
[11] Falchook GS, Moulder S, Naing A, et al. A phase I trial of combination trastuzumab, lapatinib, and bevacizumab in patients with advanced cancer. Invest New Drugs. 2015;33:177–186.
[12] Kadowaki S, Yatabe Y, Hirakawa H, et al. Complete response to trastuzumab-based chemotherapy in a patient with human epidermal growth factor receptor-2-positive metastatic salivary duct carcinoma ex pleomorphic adenoma. Case Rep Oncol. 2013;6:450–455.