First Description of a Hybrid Tumor of the Sublingual Gland

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Abstract. *Background: Hybrid tumours of the salivary glands are rare neoplasms. They are composed of at least two different tumour entities located in the same topographic area and account for only 0.1% of all salivary gland tumours. The most common component is an adenoid cystic carcinoma. There are several possible forms of hybrid tumours, which are most commonly located in the parotid gland. Case Report: We report on a 59-year-old female, who presented with a lesion of the caruncula of the left sublingual gland. The biopsy showed an adenoid cystic carcinoma in combination with a salivary duct carcinoma. Treatment consisted of tumour resection, bilateral selective neck dissection and adjuvant radiotherapy. Histopathologically, at least 30% of the tumour mass was composed of a salivary duct carcinoma and 70% of an adenoid cystic carcinoma. At 58 months after treatment, the patient is alive without evidence of recurrent disease. Conclusion: To our knowledge, the presented case is the first description of a hybrid tumour of the sublingual gland. Furthermore, the post-therapeutic course is encouraging, as hybrid tumours of the salivary glands usually have a poor prognosis.*

In 1996, Seifert and Donath described a series of five cases with salivary gland tumours containing two different types of neoplasms and called them hybrid tumours (1). Nowadays, hybrid tumours are defined as tumours consisting of at least two different tumour entities developing and merging in the same topographic area. Hybrid tumours account for up to 0.1% of all salivary gland tumours, and both benign and malignant hybrid tumours have been reported. The prevalence is 0.4% among parotid gland tumours (2). The most frequent tumour entities (Table I) are adenoid cystic carcinoma, epithelial-myoepithelial carcinoma and salivary duct carcinoma, the combination of adenoid cystic carcinoma and epithelial-myoepithelial carcinoma being the most common (1-10).

To our knowledge, the hybrid tumour presented below is the first described for the sublingual gland. The case also shows a surprisingly favourable post-therapeutic course, much in contrast to what has been reported for the majority of hybrid tumours of the salivary glands in the literature.

Case Report

A 59-year-old woman presented with an approximately 1-cm large mass at the ostium of the left sublingual gland. The swelling had existed for about six months and was neither painful nor progressing in size. Excisional biopsy revealed the occurrence of an adenoid cystic carcinoma in combination with a salivary duct carcinoma (see below).

Radical resection of the tumour with a selective bilateral neck-dissection, level I-III, was performed. The defect was covered using a microvascular forearm flap. After adjuvant radiotherapy (60 Gy), at 58 months, the patient is without any sign of recurrence or metastases.

Pathological findings. Macroscopically, the tumour was well-circumscribed, not encapsulated and consisted of a firm tumour mass within the left sublingual gland. It measured 1.7×1.0×1.0 cm^3.

Histopathologically, the tumour exhibited a combination of an adenoid cystic carcinoma and a salivary duct carcinoma (Figure 1a and b). The major component (*i.e.* the adenoid cystic carcinoma), amounting to 70% of the tumour, had a predominant tubular pattern, yet also contained some

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Table I. *Clinical features of hybrid tumours of the salivary glands. Review of the literature.*

	Age (years)	Gender	Localisation	Size (cm)	Histology	Therapy	Follow-Up	Authors, year (Ref.)
1	70	M	parotid	7×6×4	BCA/CA	Surgery	NA	*Seifert and Donath,* 1996 (1)
2	62	M	parotid	NA	BCA/AdCC	Surgery	NA	*Seifert and Donath,* 1996 (1)
3	60	M	parotid	5×2.5×3	WT/SGLA	Surgery	NA	*Seifert and Donath,* 1996 (1)
4	53	M	parotid	6×3×2	ACC/SDC	Surgery	NA	*Seifert and Donath,* 1996 (1)
5	66	F	palate	NA	EMC/AdCC	Surgery	NA	*Seifert and Donath,* 1996 (1)
6			parotid	2.5	EMC/AdCC/BCAC	NA	NA	*Ellis et al*., 1991 (22)
7	67	M	parotid	3	SDC/MC	Surgery, ND	DOD 3 y 3 mo	*Delgado et al*., 1993 (21)
8	67	F	parotid	5.5	ACC/MEC	Surgery	NED 1 y 6 mo	*Ballestin et al*., 1996 (20)
9	51	M	palate	4.5×3.0	AdCC/SDC	Surgery, ND	DOC 1 y 7 mo	*Kamio et al*., 1997 (16)
10	62	F	parotid	3	EMC/AdCC	NA	NED 1 y 8 mo	*Simpson et al*., 1997 (25)
11	53	M	parotid	6×4.5×3.5	AdCC/MEC	Surgery, RT	NED	*Croitoru et al*., 1999 (4)
12	71	M	parotid	2.9	AdCC/EMC	Surgery, ND, RT	NED	*Croitoru et al*., 1999 (4)
13	28	M	parotid	2.5×2	EMC/SDC	Surgery, RT	AWD	*Croitoru et al*., 1999 (4)
14	51	M	parotid	3.5×3	AdCC/SDC	Surgery, ND, RT	AWD	*Croitoru et al*., 1999 (4)
15	36	F	submandibular	3.5×2.5×2	SDC/AdCC	Surgery, ND, RT	AWD	*Snyder and Paulino* 1999 (8)
16	78	F	parotid	4.5×4×3	PLGA/SDC/AdCC/ACC	Surgery	NA	*Zardawi* 2000 (10)
17	58	M	parotid	2.5	EMC/MEC	NA	NA	*Chetty et al*., 2000 (3)
18	74	F	parotid	10	EMC/BCAC	Surgery, RT	NED 10 mo	*Nagao et al*., 2002 (2)
19	56	M	parotid	2	EMC/BCAC	Surgery, ND, RT	NED 2 y 7 mo	*Nagao et al*., 2002 (2)
20	73	F	parotid	2	EMC/SCC	Surgery	NED 4 y	*Nagao et al*., 2002 (2)
21	40	M	parotid	3	SDC/AdCC	Surgery, RT	NED 15 y	*Nagao et al*., 2002 (2)
22	81	F	submandibular	3	SDC/AdCC	Surgery, ND, RT	NA	*Nagao et al*., 2002 (2)
23	65	M	parotid	5	MC/SDC	Surgery, ND, RT	AWD 4 mo	*Nagao et al*., 2002 (2)
24	42	M	parotid	4	ACC/SDC	Surgery	NA	*Nagao et al*., 2002 (2)
25	66	M	parotid	3.5	SCC/SDC	Surgery, ND, RT	AWD 1 y 8mo	*Nagao et al*., 2002 (2)
26	64	F	lacrimal	5	SCC/SDC	Surgery	NED 7 mo	*Nagao et al*., 2002 (2)
27	26	F	maxillarysinus	NA	EMC/AdCC	Surgery, RT, Chemo	DOD 7 y	*Woo et al*., 2003(9)
28	49	F	palate	3.5×3.5×2.5	MEC/AdCC	Surgery, ND, RT	NED 10 mo	*Ruíz-Godoy et al*., 2003 (7)
29	71	M	palate	4×3×3	EMC/AdCC	Surgery, RT	NED 4y 1 mo	*Ruíz-Godoy et al*., 2003 (7)
30		F	parotid	4	EMC/LEC (EBV+)	Surgery, ND	NED 6 mo	*Piana et al*., 2004 (6)
31	68	F	parotid	4×4×3	AdCC/BCAC	Surgery	DOC 5 mo	*Murphy et al*., 2006 (5)
32	74	M	parotid	4.5	EMC/SDC	Surgery	NED 1 y 4 mo	*Kainuma et al*., 2010 (23)
33	65	M	upper lip	3×2.5	AdCC/EMC	Surgery	NED 3 y 4 mo	*Mosqueda-Taylor et al*., 2010 (24)
34	56	F	sublingual	1.7×1×1	AdCC/SDC	Surgery, ND, RT	NED 3 y	Our case

AdCC: Adenoid cystic carcinoma; ACC: acinic cell carcinoma; BCA: basal cell adenoma; BCAC: basal cell adeno carcinoma CA: canalicular adenoma; Chemo: chemotherapy; EBV+: Ebstein Barr Virus-positive; EMC: epithelial-myoepithelial carcinoma; LEC: lymphoepithelial carcinoma; MC: myoepithelial carcinoma; MEC: mucoepidermoid carcinoma; NA: not applicable; SDC: salivary duct carcinoma; SGLA: sebaceous gland lymphadenoma; WT: Warthin's tumour; AWD: alive with disease; DOC: died of other cause; DOD: died of disease; NED: no evidence of disease; y: year; mo: months; ND: neck dissection.

microcystic and cribriform spaces filled with basophilic mucoid material. The predominant myoepithelial cell type of this tumour component exhibited some clearing of the cytoplasm, hyperchromatic angular nuclei, and expression of the myoepithelial markers smooth muscle actin (SMA) and p63 (Figure 1c) and the basal cell marker cytokeratin (CK)5/6 (Figure 1d) by immunohistochemistry.

At least 30% of the tumour mass was composed of a high-grade carcinoma with solid and ductal (comedo-type) patterns, marked nuclear pleomorphism and a high mitotic rate, and strong cytoplasmatic expression of CK7 in addition to human epidermal growth factor receptor-2 (HER2)-expression. This tumour component was negative for SMA, and exhibited restricted CK5/6 (Figure 1d) and p63 staining (Table II). The growth fraction, as indicated by Ki67 expression was 40% in the salivary duct carcinoma and 10% in the adenoid cystic carcinoma. Both tumour components exhibited perineural invasion. The resection margins were free of tumour cells. Tissue probe processing, antibodies for immunostaining, clones, dilutions, detection system and image acquisition were performed as described by Boecker *et al*. (11).

Molecular genetic analysis aimed at examining the myeloblastosis oncogene homolog nuclear factor I/B(*MYB-NFIB*) fusion gene was negative, and for this reason, the question of a combination of an ordinary salivary duct carcinoma (with ductal carcinoma *in situ* structures) and a

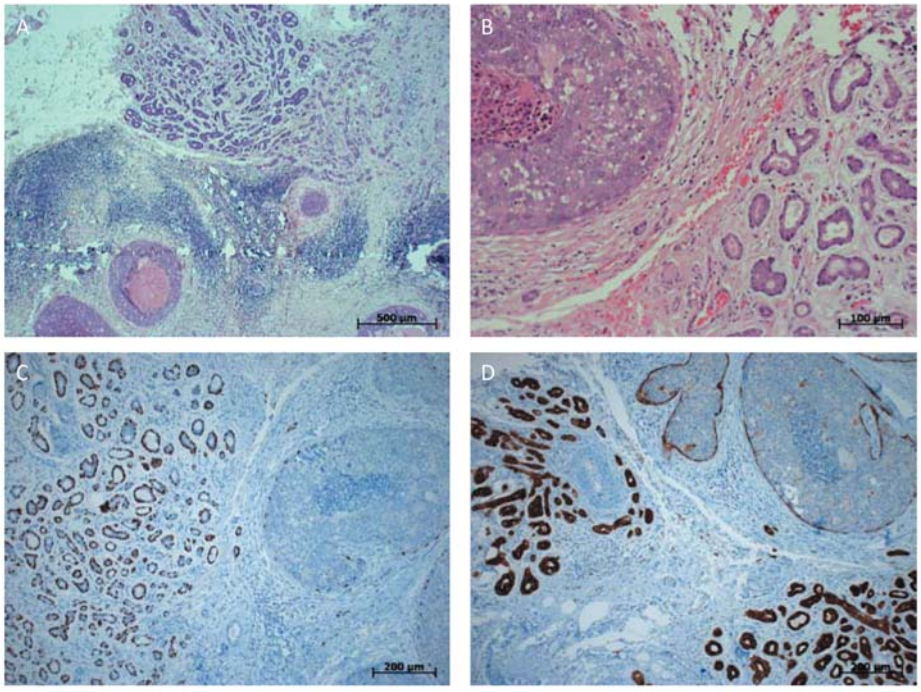

Figure 1. *A: Hybrid tumour of the sublingual gland. The component of adenoid cystic carcinoma (upper part) exhibits a predominant tubular and cribriform architecture. The salivary duct carcinoma (lower part) forms large duct-like structures with a solid pattern and central comedo-like necrosis with parafocal chronic inflammation. Hematoxylin and eosin, ×50. B: Salivary duct carcinoma (left side) with a duct filled by large, pleomorphic tumour cells in a solid pattern and central comedo-like necrosis. Adenoid cystic carcinoma (right side) is sharply demarcated with smaller tumour cells arranged in tubular and cribriform glands. HE, ×200. C: Immunohistochemical analysis showed strong expression of the myoepithelial marker p63 in the adenoid cystic carcinoma and only focal expression in the salivary duct component. ×100. D: Strong expression of cytokeratin 5/6 by immunohistochemistry in the adenoid cystic component and only weak restricted staining in the salivary duct carcinoma. ×100.*

basal-like salivary duct carcinoma variant (with strong CK5/6 staining) had to be answered [as demonstrated by Di Palma *et al*. (12)]. Yet in the tubular part of the tumour, the epithelial-myoepithelial differentiation was confirmed by SMA and p63 stainings, revealing a pattern similar to what has been recently shown to be typical for adenoid cystic carcinomas (11), and thus again favouring the existence of a hybrid tumour.

Table II. *Immunohistochemical profile.*

	Salivary duct carcinoma	Adenoid cystic carcinoma
CK7	+	+
CK5/6	–	+
SMA	–	+
p63	–	+
Her2	(+) focal	–

CK: Cytokeratin; SMA: smooth muscle actin; HER2: human epidermal growth factor receptor-2.

Discussion and Review of the Literature

Hybrid tumours of salivary glands are very rare tumours which consist of at least two distinct separable tumour entities, producing a single tumour mass (1). Hybrid tumours should not be confused with collision tumours, which arise from two different adjacent tumours. Kufeld *et al*. described a collision tumour consisting of an adenoid cystic carcinoma of the pharynx and a squamous cell carcinoma of the larynx (7, 13). These lesions should also be distinguished from tumours with bi-phasic differentiation, which are single entities composed of two different cellular types, such as epithelial-myoepithelial carcinomas and pleomorphic adenomas (7, 9, 14-17). Furthermore, there are other malignancies from which to differentiate a hybrid tumour, i.e. frome dedifferentiated tumours, as in cases of adenoid cystic carcinoma (ACC), or from those arising from a pre-existing benign tumour, as in carcinomas ex mixed tumour, an epithelial malignancy in a pleomorphic adenoma (8, 18). There are controversial views still in regard to the definition of hybrid tumour (9). Grenko *et al*. presented cases of three

adenoid cystic carcinomas and two epithelial-myoepithelial carcinomas and suggested not including these tumours in the group of hybrid tumours since they share similar myoepithelial differentiation pathways (15). These authors accepted only tumours of different cell lineages as being hybrid tumours, an example being a mixed carcinoma with and without myoepithelial differentiation (*i.e.* adenoid cystic carcinoma and mucoepidermoid carcinoma).

A similar view has been published by Chetty *et al.* (3), while Seifert and Donath (1), as well as Croitoru *et al.* (4), did not see qualitative (phenotypical) limitations when reporting on hybrid tumours. Nagao *et al.* even tried to resolve the question in a quantitative approach segregating mixed carcinomas from 'true' hybrid tumour whose carcinoma components each occupied at least 30% of the total tumor mass (2). In our case, quantification was a matter of debate, since at the beginning, it was even discussed whether the tumour was merely an adenoid cystic carcinoma with an undifferentiated basaloid (comedo-like) component within. Yet we did not find the *MYB-NFIB* fusion gene, which is typical of the majority of adenoid cystic carcinomas (19). On the grounds of phenotypical differences, we were able to decide that the salivary duct carcinoma accounted for at least 30% of the total tumour mass.

To date 33 cases of hybrid tumours in the salivary glands have been described (Table I) (1-10, 16, 20-25), the presented case being the first description of a hybrid tumour of the sublingual gland, to our knowledge. In 24 out of 33 (72.7%) cases described, the hybrid tumour occurred in the parotid gland (Table I). With respect to the tumour type, adenoid cystic carcinoma was most frequent (16/33, 48.5%), followed by epithelial-myoepithelial carcinoma (14/33, 42.5%), and salivary duct carcinoma (12/33, 36%). In our case, the hybrid tumour consisted of an adenoid cystic carcinoma and a salivary duct carcinoma. In the literature, this combination has been described in seven out of 33 cases (21%), being second to the coexistence of adenoid cystic carcinoma and epithelial-myoepithelial carcinoma.

In our case, apart from the different phenotypes, different growth rates were seen in the salivary duct carcinoma (40%) and in the adenoid cystic carcinoma (10%), as indicated by Ki67 immunohistochemistry. This difference is consistent with the findings of Nagao *et al.*(2). They described different Ki67 expression within the tumour parts in five out of nine cases. A high proliferative rate of salivary duct carcinoma was also found by Jaehne *et al.* (26). Through immunohistochemical examination of Ki67 they describe a proliferative rate of more than 25% in three quarters of the examined tumour samples of salivary duct carcinoma. Vacchi-Suzzi *et al.* showed there to be a significant difference in the survival of patients with salivary duct carcinomas depending on growth rates (27).

The 5-year survival rate for patients with adenoid cystic carcinoma is 42% (28, 29), for salivary duct carcinoma it is only 30% (30). Due to the small number of hybrid tumours reported, clinical experience is restricted and management is challenging. As for other mixed tumours, clinical/surgical oncologists follow the rule of treating according to the guidelines for the most aggressive tumour component, the primary approach of course being the surgical removal of the tumour with clear margins (5, 7, 31, 32).

Conflicts of Interest

All Authors declare that there is no conflict of interest and there was no financial support for this study.

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