Multiple Malignant Salivary Gland Neoplasms: Mucoepidermoid Carcinoma of Palate and Adenoid Cystic Carcinoma of Floor of Mouth

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Abstract Salivary gland tumors usually occur as single lesions. To have more than one tumor is unusual. We report a case of an adult male who presented with a mucoepidermoid carcinoma involving the minor salivary glands of the palate at age 57 years, followed by an adenoid cystic carcinoma of the floor of mouth at age 63 years. The patient later succumbed to non-Hodgkin lymphoma at age 72 years. There are 31 acceptable cases of multiple malignant salivary gland neoplasms reported in the world literature. Multiple malignant tumors of the same histologic type are more common than those of different histologic type. Bilateral acinic cell adenocarcinoma was the most frequent combination of multiple salivary gland malignancy, accounting for 14 cases (10 synchronous and four metachronous). All involved the parotid glands bilaterally with the exception of one case that involved parotid and submandibular gland. Polymorphous low-grade adenocarcinoma accounted for three of the four cases of multiple malignant tumors involving minor salivary glands. Individuals with a history of malignancy are at risk for the

development of additional malignant tumors and should receive appropriate clinical follow-up.

Keywords Salivary gland neoplasms · Salivary gland tumors · Multiple malignant salivary gland neoplasms · Synchronous neoplasms · Metachronous neoplasms

Introduction

The typical salivary gland neoplasm arises as a single mass localized to one salivary gland. A more unusual event is the development of multiple salivary gland neoplasms, either at the same or different times, located either in different glands, or more rarely, within the same gland [1]. Combinations of multiple salivary gland tumors have been reported, including multiple benign tumors, as well as both benign and malignant tumors [1, 2]. Even more unusual is the occurrence of multiple malignant tumors.

Seifert and Donath [1] discussed the terminology (Table 1) used to describe multiple salivary gland neoplasms. Multiple tumors may be considered from three perspectives: according to their *histologic type* (identical or different histology), *time of development* (synchronous¹ or metachronous²) and *localization* (unilateral or bilateral) [1]. The term *unilateral* may be confusing in the context of multiple salivary gland tumors. The obvious meaning is the location on one side of the body, however, this term may also be used to refer to multiple tumors occurring within the same salivary gland. For instance, “*unilateral synchronous tumors*” may refer not only to synchronous

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¹ Simultaneous or autochronous

² Asynchronous

Table 1 Nomenclature for multiple malignant salivary gland tumors [1]

Descriptor	Categories
Histologic type	Identical histology
	Different histology
Localization	Unilateral
	Bilateral
Time of development	Synchronous
	Metachronous

tumors arising in two different ipsilateral glands, but also to two distinct and separate tumors arising in the same gland at the same time. The term “*bilateral synchronous tumors*” is less ambiguous and refers to contralateral tumors arising at the same time, perhaps in the same or different paired salivary glands or minor glands. In practice, it may be problematic to definitively separate synchronicity from metachronicity. The terminology relating to localization (unilateral or bilateral) is most useful when applied to the paired major salivary glands and is less useful when applied to the non-paired minor salivary glands. Multiple minor salivary gland neoplasms may present as multicentric lesions, perhaps ipsilateral or contralateral.

When assessing synchronous primary malignant salivary gland neoplasms of identical histopathology, the possibility of there being one primary neoplasm with metastasis must be considered [3]. It is also important to keep in mind the possibility of multiple tumors arising in one gland to avoid over interpretation of this finding as evidence of a malignant growth pattern [4]. A special case that must be distinguished is the very rare occurrence of hybrid salivary gland neoplasms composed of two different tumor entities arising simultaneously at the same site from the same tissue [1], which is distinct from the exceedingly rare “collision” tumor in which two malignant tumors, arising at different sites, infiltrate each other [1].

The cause of salivary gland tumors is unknown [4]. A number of risk factors have been identified, including radiation exposure [4–8], genetic predisposition [9], tobacco use (particularly for Warthin tumor) [5, 10, 11], viruses [5, 12–15] and exposure to environmental chemicals [5]. There is a strong association with exposure to ionizing radiation and salivary gland neoplasia. Survivors of nuclear weapons exposure during World War II experienced significantly increased risk for developing both benign and malignant salivary gland tumors and the level of risk was proportional to the radiation dose received [8]. An increased incidence of salivary gland neoplasia has also been reported in patients receiving therapeutic irradiation to the head and neck [4, 6, 7]. Several studies show a relationship between

excessive use of diagnostic radiography and the development of malignant parotid tumors [4, 16].

There is also an increased risk for carcinoma of other organ systems following a primary benign or malignant salivary gland neoplasm, including breast, thyroid, bronchus and ovary [1, 4, 17], although some of the evidence is conflicting regarding the existence and exact degree of risk [4].

The purpose of this report is to document the rare occurrence of two primary, metachronous, malignant salivary gland neoplasms of different histologic type in one individual, both involving minor salivary glands. This is the fourth report of multiple malignant salivary gland neoplasms involving minor salivary glands [18, 19] and the first report of metachronous tumors of different histologic type involving minor salivary glands.

Case report

A 57 year-old Caucasian male, a retired Navy Chief Hospital Corpsman, related a one-year history of intermittent swelling of the left posterior maxilla accompanied by a draining sinus tract that was believed to represent an inflammatory lesion of odontogenic origin. He had been treated unsuccessfully with antibiotics on two occasions. After a number of interventions, including non-surgical endodontic therapy of tooth #13 and extraction of tooth #15, which were unsuccessful in resolving his symptoms, he was referred for biopsy. The left maxillary tuberosity exhibited an ulcerated, expansile, bluish mass (Fig. 1). A panoramic radiograph exhibited a radiolucent lesion with destruction of the left maxillary tuberosity (Fig. 2). The lesion had never been painful, nor were there symptoms associated with the maxillary sinus. An incisional biopsy

Fig. 1 First primary neoplasm. Intraoral clinical photograph of well-differentiated mucoepidermoid carcinoma presenting as an ulcerated, bluish mass expanding the left maxillary tuberosity. This image was published in Surgical pathology of the salivary glands, Ellis GL, Auclair PL, Gnepp DR, page 275, Fig. 16–2B, Saunders, 1991

Fig. 2 First primary neoplasm. Preoperative panoramic radiograph exhibiting a lucent lesion involving the left maxillary tuberosity, associated with a well-differentiated mucoepidermoid carcinoma. Tooth #15 has been extracted and tooth #13 has been treated endodontically

was diagnostic for low-grade mucoepidermoid carcinoma. The lesion was treated surgically by a left hemi-maxillectomy and the surgical defect was treated with a removable obturator appliance.

The surgical specimen exhibited a low-grade mucoepidermoid carcinoma invading the bone of the maxillary alveolar process (Fig. 3). The tumor exhibited prominent mucin-filled cystic spaces lined by well-differentiated neoplastic epithelium that formed a number of papillary structures composed of columnar mucous cells and intermediate cells. Associated areas exhibited sheets of epidermoid and mucous cells that exhibited positive staining for cytoplasmic mucin (Fig. 4).

Fig. 3 First primary neoplasm. Photomicrograph of low-grade mucoepidermoid carcinoma infiltrating the bone of the left maxillary tuberosity (right). The tumor exhibits cystic spaces lined by well-differentiated epithelium forming papillary structures composed of columnar mucous cells and intermediate cells (center) and sheets of epidermoid and mucous cells (lower left). (Hematoxylin and eosin stain. Original magnification $\times 200$)

Fig. 4 First primary neoplasm. Photomicrograph exhibiting a sheet of epidermoid and mucous cells that exhibit positivity for cytoplasmic mucin. Also present are a number of cells with clear cytoplasm. (Mucicarmine stain. Original magnification $\times 400$)

The patient was free of disease until the sixth year of follow-up, when at the age of 63 years, an asymptomatic, 2.0×1.0 cm, firm nodule was noted along the lingual surface of the mandible in the right floor of mouth (Fig. 5). An excisional biopsy was diagnostic for adenoid cystic carcinoma, consisting of small, basaloid cells arranged in cribriform nests and sheets invading the surrounding connective tissue (Fig. 6). Although the tumor was believed to have most likely arisen from minor salivary gland tissue, the primary site of origin of the tumor could not be determined with absolute certainty based on the surgical material and origin from the sublingual gland could not be definitively excluded. Subsequently, the area was treated by wide local excision, including a marginal resection of the mandibular cortex with associated teeth, an *en bloc* neck dissection and by post-operative radiation therapy.

At the age of 68 years the patient presented with inguinal lymphadenopathy and was diagnosed with non-Hodgkin lymphoma of unknown type. After treatment with a course of chemotherapy, he remained in remission for four years. Subsequently, a recurrence of the lymphoma in his neck was treated with radiation therapy. He died of complications related to lymphoma at the age of 72 years. An autopsy was not performed.

Discussion

There are 31 acceptable cases of multiple malignant salivary gland neoplasms reported in the world literature (Table 2). We focused our review specifically on cases involving multiple malignant salivary gland tumors, rather

Fig. 5 Second primary neoplasm. Diagram depicting the floor of the mouth showing the clinical location of adenoid cystic carcinoma, arising as a nodule in the mucosa of the right floor of mouth along the lingual surface of the mandible

Fig. 6 Second primary neoplasm. Photomicrograph exhibiting adenoid cystic carcinoma, consisting of cribriform nests and sheets of small, basaloid cells infiltrating the adjacent connective tissue. (Hematoxylin and eosin stain. Original magnification $\times 100$)

than expanding it to include the broader context of all combinations of multiple benign and multiple benign and malignant tumors. The last such comprehensive review of

multiple salivary gland tumors of all combinations was reported by Gnepp et al. in 1989 [2]. In the interim, there were 11 additional reports of multiple malignant salivary gland tumors [19, 27, 28, 35–37, 39, 40, 42, 45].

We excluded a number of reports cited by other reviewers. The lesions reported by Nelson et al. [46] as bilateral acinic cell adenocarcinomas were excluded because, like Gnepp et al. [2] we believe that they represent bilateral clear cell oncocytomas. Likewise, the tumors reported by Nuutinen et al. [40] may also represent bilateral clear cell oncocytomas although we included this case since the report contained insufficient information to make a definitive determination. The case reported by Schroeder and Droese [41] as salivary duct carcinoma represents an example of epithelial myoepithelial carcinoma and we included it as such, as did Seifert and Donath [1]. The case reported by Appel et al. [18] as multifocal adenoid cystic carcinoma is a polymorphous low-grade adenocarcinoma and is recorded as such. As Gnepp et al. [2] observed, the lesions reported by Arsac et al. [20] as cylindromas may represent basal cell adenoma variants, although there is insufficient information available to make a definitive determination and we have included these lesions as adenoid cystic carcinomas. We excluded the case reported by Bauer and Bauer [47], although others have recorded it as an example multiple acinic cell adenocarcinoma [3, 25, 30, 32]. Gnepp et al. [2] believe this lesion represents a bilateral oncocytoma or oncocytosis. We excluded the case reported by De la Pava et al. [48] as multifocal carcinoma since it represents a multifocal canalicular adenoma. We believe the synchronous bilateral tumors reported by Ferlito [33] as trabecular adenocarcinomas are best classified as carcinoma ex pleomorphic adenoma and adenocarcinoma, NOS by contemporary WHO terminology and have included them as such. The origin of one of their tumors from a pre-existing pleomorphic adenoma is not clear from their abstract due to a typographic error, although their following case report makes this clear. We also excluded the case reported by Brousset et al. [45] of a tumor arising from the minor salivary glands of the palate. The authors concluded that the two distinct histologic patterns in their tumor, adenoid cystic carcinoma and clear cell carcinoma, arose from a common focus. Their images show that the two tumor types are intricately involved, with transitional areas and there is no evidence of separation that would indicate that two separate malignant lesions arose on the palate and collided. This lesion may represent a very rare hybrid neoplasm.

Multiple malignant salivary gland neoplasms of the same histologic type are much more common than those of different histologic type. Twenty-five of the cases involve tumors of the same histologic type and only six cases involve tumors of different histologic types. Three of the

Table 2 Previously reported cases of synchronous and metachronous multiple malignant salivary gland neoplasms, including the present case

Author	Temporality	Glands	Histologic type	Age and gender	Comment
Appell et al. [18]	syn	Minor/Minor	PMLGA/PMLGA	62 F	
Arsac et al. [20]	Meta–5y	Parotid/Parotid	AdCystic/AdCystic	69 F	
Assor et al. [21]	Meta–18 m	Parotid/Parotid	AdenoCa (PD)/SCCa (ex WT)	58 M	Recorded as acinic cell carcinoma by others [1]
Berkeley [22] Case 3	syn	Parotid/Parotid	AdenoCa/AdenoCa	5 M	Associated with nevus sebaceous
Catania et al. [23]	syn	Parotid/Parotid	MucoEp/MucoEp	46 F	
Chong et al. [24]	syn	Parotid/Parotid	AcinicCell/AcinicCell	NR	Recorded as two cases by others [25]
Clarke et al. [26]	syn	Parotid/Parotid	AcinicCell/AcinicCell	20 F	
Clayton et al. [19] Case 1	syn	Minor/Minor	PMLGA/PMLGA	68 M	
Clayton et al. [19] Case 2	syn	Minor/Minor/Minor	PMLGA/PMLGA	70 M	Three minor salivary glands of upper lip
Delides et al [27]	syn	Parotid/Parotid	AcinicCell/AcinicCell	64 M	Familial, synchronous with pituitary adenoma
Di Palma et al. [28]	Meta–1y	Parotid/Parotid	AcinicCell/AcinicCell	35 F	One tumor with dedifferentiated component
Diamant et al. [29] Case 1	syn	Parotid/Parotid	AcinicCell/AcinicCell	71 M	Discussed by Eneroth [30]
Diamant et al. [29] Case 2	syn	Parotid/Parotid	AcinicCell/AcinicCell	55 F	Discussed by Eneroth [30]
Dunn et al. [31]	syn	Parotid/Parotid	AcinicCell/AcinicCell	32 F	Dead of disease at 8 months
Eneroth et al. [32]	Meta–15 y	Parotid/Parotid	AcinicCell/AcinicCell	27 U	
Ferlito [33]	syn	Parotid/Parotid	AdenoCa/CaExPA	67 M	Reopoted as trabecular adenocarcinomas
Gnepp et al. [2]	syn	Parotid (same gland)	BCAdenoCa and AdCystic/EMC	70 M	Discussed by Corio [34]
Gnepp et al. [2]	syn	Parotid (same gland)	AdCystic and SebaceousCa	NR	Refer to footnote in discussion section
Gustaffson and Carlsoo [3]	syn	Parotid/SMG	AcinicCell/AcinicCell	75 M	
Habuka and Hyodo [35]	syn	Parotid/Parotid	MucoEp/MucoEp	48 M	
Hardee et al. [36]	Meta–2 y	SMG/SMG	AdenoCa/AdenoCa	31F	Dead of disease at 46 months
Hosni et al. [37]	Meta–4 y	Parotid/SMG	MucoEp/AdCystic	56 M	
Levin et al. [25]	syn	Parotid/Parotid	AcinicCell/AcinicCell	57 F	
McGrath [38]	syn	Parotid/SMG	CaExPA/CaExPA	56 M	Intracapsular carcinoma ex pleomorphic adenoma
Millar et al. [39]	syn	Parotid/Parotid	AcinicCell/AcinicCell	77 F	
Nuutinen et al. [40]	Meta–3 y	Parotid/Parotid	AcinicCell/AcinicCell	55 F	
Schroder and Droese [41]	Meta–1 y	Parotid/Parotid	EMC/EMC	36 F	
Seifert [42]	Meta–U	Parotid/Parotid	MucoEp/MucoEp (both ex WT)	73 M	
Turnbull and Frazell [43] Case 1	syn	Parotid/Parotid	AcinicCell/AcinicCell	36 F	Discussed by Spiro et al. [44]
Turnbull and Frazell [43] Case 2	Meta–8 y	Parotid/Parotid	AcinicCell/AcinicCell	60 M	PA of SMG. discussed by Spiro et al. [44]
Whitt et al. (present case)	Meta–5 y	Minor/Minor	MucoEp/AdCysticCa	57 M	Died of non-Hodgkin lymphoma at age 72 y

Key to abbreviations AcinicCell = Acinic cell adenocarcinoma, MucoEp = Mucoepidermoid Carcinoma, AdenoCa = Adenocarcinoma, NOS, AdCystic = Adenoid Cystic Carcinoma, EMC = Epithelial Myoepithelial Carcinoma, SCCa = Squamous Cell Carcinoma, WT = Warthin tumor, BCAdenoCa = Basal Cell Adenocarcinoma, PMLGA = Polymorphous Low Grade Adenocarcinoma, PA = Pleomorphic Adenoma, CaExPA = Carcinoma ex Pleomorphic Adenoma, SebaceousCa = sebaceous carcinoma, U = Unknown, NR = not reported, syn = synchronous, meta = metachronous, M = male, F = female, y = years, m = months, PD = poorly differentiated, SMG = submandibular gland

Table 3 Time of development of multiple malignant salivary tumors versus histologic type

	Same histology	<i>n</i>	Different histology	<i>n</i>
Synchronous	Acinic cell adenocarcinoma–[3, 24–27, 29, 31, 39, 43]	10	Basal cell adenocarcinoma and adenoid cystic carcinoma/epithelial myoepithelial carcinoma–[2] (<i>same gland</i>)	1
	Polymorphous low grade adenocarcinoma–[18, 19]	3	Adenoid cystic carcinoma and sebaceous carcinoma - [2] (<i>same gland</i> , refer to footnote in discussion section)	1
	Mucoepidermoid carcinoma–[23, 35]	2	Carcinoma ex pleomorphic adenoma and adenocarcinoma, NOS–[33]	1
	Adenocarcinoma, NOS–[22]	1		
	Carcinoma ex pleomorphic adenoma–[38]	1		
Metachronous	Acinic cell adenocarcinoma–[28, 32, 40, 43]	4	Mucoepidermoid carcinoma and adenoid cystic carcinoma–[37], Whitt et al. (present case)	2
	Adenoid cystic carcinoma–[20]	1	Adenocarcinoma, NOS and squamous cell carcinoma (ex PCL)–[21]	1
	Mucoepidermoid carcinoma (ex Warthin tumor)–[42]	1		
	Adenocarcinoma, NOS–[36]	1		
	Epithelial myoepithelial carcinoma–[41]	1		

Key to Abbreviations *n* = number of tumors

four minor salivary gland cases were also of the same histologic type (Table 3). The more common occurrence of tumors of the same histologic type suggests the possibility of a common genetic risk factor, rather than a purely random event.

Bilateral acinic cell adenocarcinoma was the most frequent combination of multiple salivary gland malignancy, accounting for 14 cases (10 synchronous [3, 24–27, 29, 31, 39, 43] and four metachronous [28, 32, 40, 43]). Levin et al. [25] recorded three additional unpublished cases of bilateral acinic cell adenocarcinoma of parotid, without commenting on temporality and reported a rate of bilaterality as high as 3%. All cases of bilateral acinic cell adenocarcinoma involved the parotid glands with the exception of one case that involved parotid and submandibular gland. Familial occurrence of acinic cell adenocarcinoma has been reported [49], including a patient with synchronous, bilateral parotid gland acinic cell adenocarcinomas [27] and a sibling with bilateral parotid tumors, one of which was acinic cell adenocarcinoma. Familial occurrence might represent a coincidental event or may be related to common genetic or environmental risk factors [27, 49].

The major salivary glands are involved by multiple malignant salivary gland tumors much more frequently than the minor salivary glands. Twenty-seven cases involved only the major salivary glands and four cases involved only minor salivary glands (Table 4). Polymorphous low-grade adenocarcinoma accounted for three of the four minor salivary gland cases that were of the same histologic type. We believe that the site of origin of the

second primary malignancy in our reported case was from minor salivary gland tissue in the floor of the mouth rather than from the sublingual gland although we were unable to determine this with absolute certainty. Therefore, this case is the first report of multiple malignant neoplasms of different histologic types arising in minor salivary gland tissue.

Multiple malignant salivary gland tumors are more likely to arise synchronously than metachronously. In 20 of the reports, the tumors were identified synchronously and in 11 of the cases, the second primary malignant tumor was identified metachronously. The mean interval between the first primary and the second primary tumor was 4.5 years, with a range of 1 year to 15 years (the interval was not reported for one case). Two cases involved unilateral synchronous major salivary gland tumors (multiple malignant tumors in one salivary gland) [2]. Both reports involved the parotid gland and both were of dissimilar histologic type³.

As would be expected for malignant salivary gland neoplasms in general, the mean age for the first primary tumor is in an older age group, although one case was reported in a five year-old child [22]. The mean age for patients with multiple malignant salivary gland neoplasms at the time of their first primary tumor was 53 years, with a range of 5 years to 72 years (age was not recorded for two

³ We were unable to locate the source of the report of unilateral synchronous adenoid cystic carcinoma and sebaceous adenocarcinoma of parotid gland in Table 3 of Gnepp et al. [2] due to a typographic error in the published citation.

Table 4 Location of multiple malignant salivary tumors versus histologic type

Synchronous occurrence				
Parotid (same gland)	Parotid–Parotid	Parotid–SMG	SMG–SMG	Minor–Minor
<i>BCAC and AdCystic/EMC</i>	<i>Acinic–Acinic</i>	<i>Acinic–Acinic</i>		<i>PMLG–PMLG</i>
Gnepp et al. [2]	Clarke et al. [26]	Gustafsson and Carlsoo [3]		Appell et al. [18]
<i>AdCystic and SebaceousCa</i>	Delides et al. [27]	<i>CaExPA–CaExPA</i>		Clayton et al. [19] Case 1
Gnepp et al. [2] (refer to footnote in discussion section)	Diamant et al. [29] Case 1	McGrath [38]		Clayton et al. [19] Case 2 (three tumors)
	Diamant et al. [29] Case 2			
	Dunn et al. [31]			
	Levin et al. [25]			
	Millar et al. [39]			
	Chong et al. [24]			
	Turnbull and Frazell [43]			
	<i>MucoEp–MucoEp</i>			
	Habuka and Hyodo [35]			
	Catania et al. [23]			
	<i>AdenoCa–AdenoCa</i>			
	Berkeley [22] Case 3			
	<i>CaExPA–AdenoCa</i>			
	Ferlito [33]			
Metachronous Occurrence	<i>Acinic–Acinic</i>	<i>MucoEp–AdCystic</i>	<i>AdenoCa–AdenoCa</i>	<i>MucoEp–AdCystic</i>
	Di Palma et al. [28]	Hosni et al. [37]	Hardee et al. [36]	Whitt et al. (present case)
	Eneroth et al. [32]			
	Nuutinen et al. [40]			
	Turnbull and Frazell [43]			
	<i>AdCystic–AdCystic</i>			
	Arsac et al. [20]			
	<i>MucoEp–MucoEp (ex WT)</i>			
	Seifert [42]			
	<i>AdenoCa–SCCa (ex WT)</i>			
	Assor [21]			
	<i>EMC–EMC</i>			
	Schroeder and Droese [41]			

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reports). The most frequent age (mode) was 70 years. With respect to gender, there was an essentially equal distribution, with 15 cases recorded in males and 13 in females (gender was not recorded for three reports).

In summary, multiple malignant salivary gland tumors are most likely to synchronously involve the parotid glands bilaterally and be of the same histologic type, most commonly acinic cell adenocarcinoma. When a salivary gland neoplasm is identified, a thorough examination should be carried out to identify possible synchronous tumors in other glands. Individuals with a history of malignancy are at risk,

albeit low, for the development of metachronous malignant tumors and should receive appropriate clinical follow-up.

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