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Case Report Open Access

Salivary Duct Carcinoma in Minor Salivary Glands: Report of Two Cases with Different Clinical Behavior

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Abstract

Salivary duct carcinoma (SDC) is a malignant epithelial tumor extremely rare in minor salivary glands. This manuscript describes two cases of SDC of the minor salivary glands with different clinical behaviors. The first patient was an 80-year-old man who had SDC (T1N0M0) in the upper buccal fornix and the second patient was a 64-year-old man with a tumor (T2N2cM0) in the soft palate. Patients were treated with radical surgical resection and none patient underwent postoperative radiotherapy or chemotherapy. Histopathologically, the lesions showed proliferation of ductal cells with varying degrees of nuclear pleomorphism arranged in solid and cribriform structures and prominent comedonecrosis. The patient with SDC in the soft palate developed metastases and died shortly after diagnosis while the patient with SDC in upper alveolar ridge is alive without disease for over 6 years of follow-up. Although SDC is aggressive, anatomical site and precocious diagnosis are relevant factors for better prognosis.

Keywords: Salivary duct carcinoma; Minor salivary gland; Alveolar ridge; Soft palate

Introduction

Salivary duct carcinoma was first described in 1968 by Kleinsasser et al., [1] and it was recognized in the World Health Organization classification of salivary gland tumors in 1991 [2]. SDC is an uncommon and high-grade malignant tumor occurring predominantly in major salivary glands [3,4] with predilection for elderly men [5,6]. SDC is infrequent in minor salivary glands having resemblance to the ductal carcinoma of breast. SDC arises de novo or develops as the malignant component of carcinoma ex pleomorphic adenoma. SDC has invasive growth resulting in early regional and distant metastasis including lungs, liver and bones [4,7], and nearly 50% of the patients die of the disease within 4 to 5 years [8,9].

We report two cases of SDC arising of the minor salivary glands with different clinical behaviors.

Case reports

Case 1

An 80-year-old man was referred to the Oral Diagnostic Clinic for evaluation of a lesion in left upper buccal fornix with two months of evolution. On clinical examination, it was observed a painless ulcerated nodule with 2.0 x 1.0 cm that impeded the proper use of upper prosthesis (Figure1A).

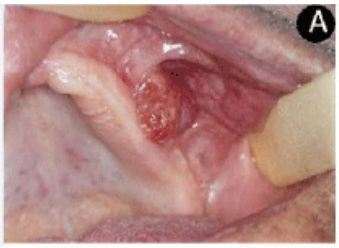

Figure 1A: Nodular lesion in the superior buccal fornix.

Medical history revealed that the patient had a prostate cancer surgically removed 8 years ago. Computed Tomography (CT) revealed a large osteolytic lesion without defined limits located in the left posterior maxilla without involvement of maxillary sinus (Figure 1B).

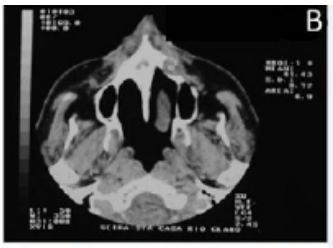

Figure 1B: CT scan axial view showing osteolytic lesion located.

The patient underwent incisional biopsy and the histopathological examination showed large and polygonal cells with eosinophilic cytoplasm containing prominent nucleoli arranged in cribriform and papillary pattern. Mitotic figures and prominent comedonecrosis were also noted highly suggestive of salivary duct carcinoma (Figure 1C and 1D).

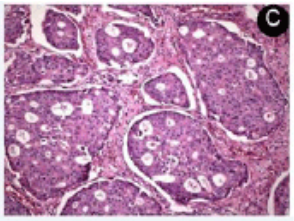

Figure 1C: Island of tumor cells arranged in a cribriform pattern (H&E staining, original magnification 100x).

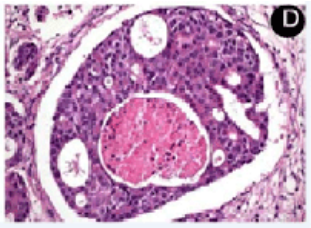

Figure 1D: Large and polygonal with eosinophilic cytoplasm containing prominent nucleoli, mitotic figures and comedonecrosis (H&E, original magnification 400x).

Absence of hemorrhage and perineural and vascular invasion were observed. No invasion to surrounding tissue was found. Immunohistochemical study confirmed the luminal epithelial nature of the tumor cells with strong staining for CK7, CK8, CK18, CK19 and PSA (Figure 2).

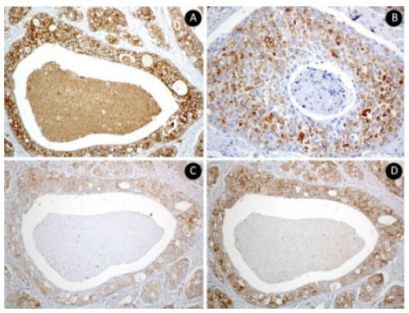

Figure 2: Immunohistochemical study confirmed the luminal epithelial nature of the tumor cells with diffuse strong staining for CK7 (A), CK8 (B), CK18 (C) and CK19 (D) (high magnification 400x).

It was observed negativity for p63. The Ki-67 index in the tumoral cells was 5%.

The patient was referred to the head and neck surgeon who requested chest x-ray, gastrointestinal endoscopy, prostate ultrasound, bone scintigraphy and laboratory tests (PSA), which ruled out the possibility of metastasis or other primary tumors. The patient was staged as T1N0M0 and a maxillectomy was performed. The specimen measured 1.8x1.0 cm and the histopathologic analysis of the surgical specimen confirmed the diagnosis of SDC and showed free surgical margins. The tumor was well delimited. At six years of follow-up, the patient is alive without evidence of recurrence or metastasis.

Case 2

A 64-year-old man was referred complaining of a painless nodule in the palate for five months. Extraoral evaluation revealed cervical lymph nodes bilaterally suggestive of metastasis. On intraoral examination it was observed a nodular lesion involving the soft palate, measuring approximately 3.0x2.5 cm displacing the uvula to the right side (Figure 3A and 3B).

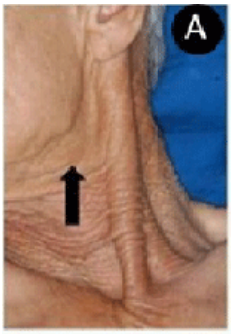

Figure 3A: Arrow showing enlarged lymph node.

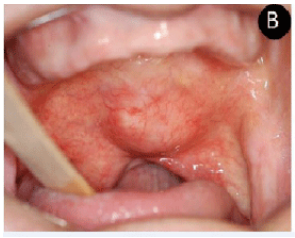

Figure 3B: Nodular lesion on the soft palate causing displacement of the uvula

The patient underwent incisional biopsy and the microscopical findings showed a proliferation of carcinomatous islands and scattered individual cells immersed in a highly hyalinized connective tissue. The neoplastic cells formed solid islands in a ductal pattern. The luminal cells were eosinophilic with hyperchromatic nuclei and conspicuous central nucleoli. The diagnosis was of invasive adenocarcinoma.

The patient was referred to head and neck surgeon, who staged the patient as T2N2cM0 (TNM system) through image examination (CT). The surgeon performed a radical tumor resection with bilateral neck dissection. The histopathological analysis of surgical specimen

revealed that the tumor consisted of solid and cribriform cell nests with ductal structures, comedonecrosis, frequent mitoses and intense neural and vascular invasion allowing the final diagnosis of SDC (Figure 3C).

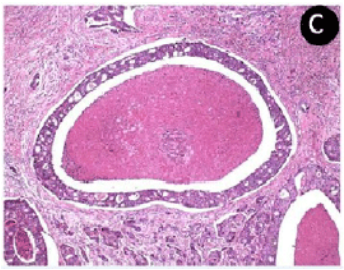

Figure 3C: Tumor cell with comedonecrosis (H&E, original magnification 100x).

The immunohistochemical findings were the same case 1: positivity for CK7, CK8, CK18, CK19 and PSA, negativity for p63 and Ki-67 index in the tumoral cells was 10%.

However, the patient died after one month.

Discussion

Salivary duct carcinoma is uncommon and aggressive adenocarcinoma that occurs almost exclusively in the major salivary glands. Reports of SDCs involving minor salivary glands of the oral cavity are rare (Table 1) [1,5,6,10-29].

Author	Age/ Gender	Site	Size (cm)	Clinical status (UICC)	Treatment	Follow-Up
Kleinsasser et al. [1]	57/M	Hard palate	"Hazelnut in size"	NI	Extirpation	NI
Chen [10]	60/F	Tongue	"Lump"	NI	Wide excision	NED 5 years
Pesce et al. [11]	62/F	Oral vestibule	1.5	NI	Excision	NI
Zohar et al. [12]	47/M	Upper lip	1	NI	Wide excision	NED 2 years
Watatani et al. [13]	60/F	Tongue	0.4	T1N0M0	Wide excision	NED 4 years
Kumar et al. [14]	NI (2 cases)	Maxilla	NI	NI	NI	NI
Delgado et al. [15]	42/M	Hard palate	3	T2N0M0	Maxillectomy	DOD 5.2 years
Epivatianos et al. [16]	80/M	Upper vestibular sulcus	2.5	T2N0M0	Maxillectomy	NI
	74/M	Lower vestibular sulcus	4	T2N2cM0	Wide excision-ND	DOD 2 years
	58/M	Hard palate	4	T2N2bM0	RT	DOD 6 months
	60/M	Buccal sulcus	3	T2N0M0	Maxillectomy-ND-RT	NED 4 years
Yoshimura et al. [5]	62/M	Buccal mucosa	3.1	T2N2bM0	Radical surgery-RT	Alive after 1.6 years with multiple metastases
Tatemoto et al. [6]	58/F	Hard palate	1	T1N0M0	Local resection	NED 2.5 years
Guzzo et al. [17]	NI	Cheek	NI	TxN0M0	Enucleated	Alive with disease (54 months)
Suzuki & Hashimoto [18]	56/M	Mandible	4	NI	Excision	NED 5 years
Lopes et al. [19]	63/M	Hard palate	6	T4N2bM0	Hemimaxillectomy-ND-RT	DOD 11 months
Huh et al. [20]	61/M	Hard palate	5	T3N0M0	Hemimaxillectomy-ND-RT	NED 9 months
	54/M	Hard palate	5	T3N0M0	Hemimaxillectomy	NED 15 months
	23/F	Hard Palate	4	T4N0M1	Patient denied further treatment	DOD 7 months
Van Heerden et al. [21]	53/F	Hard palate and right alveolar ridge	14	T4N-M0	Patient refused treatment	Lost to follow-up

	71/M	Hard palate and buccal sulcus	5	T4N-M0	Patient refused treatment	Lost to follow-up
	57/M	Hard palate	6	T4N-M0	Patient refused treatment	Lost to follow-up
	63/F	Hard palate	7	T4N-M0	Hemimaxillectomy-ND-RT	NED 10 Months
	47/M	Hard palate	5	T4N-M0	Patient still considering surgical treatment	NI
Cheuk et al. [22]	44/F	Buccal mucosa	1.2	T1N0M0	Local excision	NED 4 years
Ide et al. [23]	45/F	Retromolar gingiva	1.5	T1N0M0	Local excision	NED 11 years
Jaehne et al. [24]	NI (5 cases)	NI	NI	stage II (n=1), stage IV(n=4)	NI	NED (20%), DOD (80%)
Ponniah et al. [25]	26/M	Hard palate	3	T2N0M0	Local excision	NED 4 years
Suzuki et al. [26]	64/F	Tongue	1.5	T1N0M0	Partial glossectomy	NED 2.5 years
Kikuchi et al. [27]	62/M	Mandible	ND	stage III	Hemimandibulectomy-ND-RT-ChT	NED 5 years
Dhanuthai et al. [28]	NI	Alveolar mucosa	NI	NI	NI	NI
Thamilselvi et al. [29]	35/F	Soft palate	5.5	T3N0M0	Local excision	NI
Present cases	80/M	Buccal fornix	1	T1N0M0	Hemimaxillectomy	NED 6 years
	64/M	Soft palate	3	T2N2cM0	Radical tumor resection-ND	DOD 1 month

ChT, chemotherapy; DOD, died of disease; F, female; M, male; N/A, not available; ND, neck dissection; NED, no evidence of disease; RT, radiotherapy; NI, no information.

Table 1: Salivary duct carcinoma in minor salivary gland in the English-language literature

To the best of our knowledge, only 37 cases of SDC originating in the intraoral minor salivary glands have been reported in the English-language literature. The most frequent site is the hard palate (14 cases). We related the first case of SDC in the buccal fornix and the second case of SDC in the soft palate. SDC most frequently affects older male patients in the fifth or sixth decade of life [30]. The mean age of the current patients was 72 years (64 and 80 years) and both patients were male.

Salivary duct carcinoma can occur *de novo* or as the malignant component of carcinoma ex pleomorphic adenoma [31]. SDC can be classified into three subtypes, according to intraductal or infiltrative predominance: 1) predominantly intraductal, where 90% of the tumor is intraductal; 2) predominantly infiltrative, when less than 20% of the tumor is intraductal; or 3) infiltrative, when the tumor is entirely infiltrative [15]. After histopathological analysis of the 2 presented cases, we noted that both cases were predominantly intraductal corresponding to the more frequent subtype.

Salivary duct carcinoma shows a remarkable resemblance to ductal carcinoma of the breast [15,32,33]. Because of this similarity, after the biopsy in the current cases and given a diagnosis of SDC, the possibility of metastatic breast carcinoma was excluded because the current patients were male. In female patients, studying estrogen, progesterone receptors and immunohistochemical analysis for HER-2 protein may be contributive [34]. In addition, SDC must be differentiated from other malignant salivary gland tumors, including high-grade mucoepidermoid carcinoma, adenoid cystic carcinoma and oncocytic carcinoma [19,32,35].

The main microscopic finding includes an intraductal component, comprising proliferating ductal cells with varying degrees of nuclear pleomorphism arranged in architectural patterns including solid, "Roman bridge", papillary and cribriform structures, often with prominent comedonecrosis [33]. The stroma is densely fibrous or desmoplastic. Angiolymphatic, perineural and bone invasion are common [4,36,37].

Immunohistochemical studies can confirm the luminal epithelial nature of the tumor cells [38]. SDC is immunoreactive for low- and high-molecular-weight cytokeratin. It was shown by immunohistochemical analysis performed in case 1 of the current study. Tumor cells had diffuse strong reactivity for cytokeratin CK7, CK8, CK18 and CK19. In addition, SDC is immunoreactive for Carcinoembryonic Antigen (CEA), Epithelial Membrane Antigen (EMA) [4,15], strong nuclear reactivity for Androgen Receptors (AR) [32] and high proliferative activity for MIB1 (Ki-67) [3,8]. SDC cells are negative for S-100 protein, myoepithelial markers, estrogen and progesterone receptors. Most SDC cells have positive distinct membrane staining for HER-2/neu protein [39,40] and show variable expression for prostatic markers [41].

The invasive nature of salivary duct carcinoma requires radical surgical treatment. Adjuvant radiotherapy or chemotherapy may be indicated and is based particularly on the postoperative pathologic findings such as grade of malignancy, bone or perineural invasion [42]. Insufficient resection with positive margins, perineural invasion, lymphatic embolism, lymphatic invasion, local or regional recurrence and metastasis are factors of poor prognosis [24,43-45]. Local recurrence occurs in 35-66% of patients and distant metastasis in

50-70%, [4,17] and the more common sites are lungs, bone, brain, skin, liver and thyroid gland [46-48]. Approximately 50% of the patients die of the disease within 4 to 5 years [8,9,49]. In the case 2, the patient developed bilateral cervical lymph node metastasis probably because the size and the site of primary tumor affecting the soft palate close to the midline. These facts favored the tumor spread and consequently a poor prognosis.

Carcinomas of minor salivary glands are staged (TNM system) according to their anatomic site of origin, similar to other carcinomas [50]. Spiro et al. (1991) [51] have applied the criteria used for squamous cell carcinoma to mucoepidermoid carcinoma of minor salivary glands. Thus, the patients reported were classified as Stage I or T1N0M0 (case 1) and Stage IVA or T2N2cM0 (case 2).

In the current study, both patients were treated with radical surgical excision. The patient of the case 1 diagnosed with SDC in upper buccal fornix had no local or distant metastases and is free of disease with more than 6 years of follow-up. The patient of the case 2 who had SDC in the soft palate, besides the resection of the primary tumor, also underwent bilateral neck dissection with confirmed lymph node metastasis. No adjuvant therapy was performed because the patient died shortly.

Local invasion, frequent lymphatic and hematogenous metastasis, and poor prognosis characterize the biologic behavior of salivary duct carcinoma. Several studies have described some correlation of prognosis to tumor size (less than 3 cm indicated a better prognosis) [2]. Zohar et al. (1988) showed the highly aggressive biological behavior of the tumor when occurring in the major salivary glands, in contrast to the benign course of the salivary duct carcinoma in the minor salivary gland.

In summary, SDC is an uncommon tumor in minor salivary glands. Although, it is aggressive and has high possibility of developing local and distant metastasis, besides several factors, anatomical location and clinical stage of the tumor are relevant and may interfere with the clinical course of the tumor.

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