NUT Midline Carcinoma of the Sublingual Gland: Clinical Presentation and Review

Nolan B. Seim¹ · Ramez H. W. Philips² · Lynn Schoenfield³ · Theodoros N. Teknos¹ · James W. Rocco¹ · Amit Agrawal¹ · Enver Ozer¹ · Ricardo L. Carrau¹ · Stephen Y. Kang¹ · Matthew O. Old^{1,4}

Received: 3 February 2017 / Accepted: 11 March 2017 / Published online: 27 March 2017
© Springer Science+Business Media New York 2017

Abstract NUT midline carcinoma (NMC) is a rare and aggressive disease encountered in the midline of the head and neck or mediastinum. Due to its sparse incidence and subtle pathologic features, we aim to increase knowledge and awareness for this pathologic entity. We present an exemplary case of a young, healthy male presenting with oral cavity pain and cervical lymphadenopathy. This patient was initially diagnosed with an unspecified, highly aggressive sublingual gland malignancy and underwent locoregional resection with free flap reconstruction however suffered a rapid local recurrence and widely extensive metastasis within just 1 month. After rigorous analysis, final pathologic diagnosis revealed a poorly differentiated carcinoma with evidence of squamous differentiation that eventually, post-mortem tested positive for NMC. Only one

prior case of sublingual gland NMC has been previously reported as we discuss the literature regarding all sublingual gland malignancies as well as the pathologic features and treatment options for NMC. We recommend consideration of testing for the NUT proto-oncogene at the time of biopsy in the clinical setting of a poorly differentiated midline carcinoma, especially with squamous differentiation, of the head or neck in order to identify patients for clinical trial enrollment and appropriately counsel on the poor clinical prognosis. Improving clinician awareness is critical to increase diagnostic accuracy and need to study prospective treatment outcomes as the first step toward improving management of this difficult disease.

Keywords Head and neck cancer · Oral cancer · Undifferentiated carcinoma · Sublingual salivary gland · Floor of mouth

Presented at AHNS 9th International Conference on Head and Neck Cancer.

✉ Matthew O. Old
matthew.old@osumc.edu

¹ Department of Otolaryngology-Head and Neck Surgery, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University Wexner Medical Center, 4000 Eye and Ear Institute, 915 Olentangy River Road, Columbus, OH 43212, USA

² The Ohio State University College of Medicine, 370 W. 9th Ave, Columbus, OH 43210, USA

³ Department of Pathology, The Ohio State University Wexner Medical Center, Doan Hall, N337B, 410 West 10th Ave., Columbus, OH 43210, USA

⁴ Department of Otolaryngology-Head and Neck Surgery, The James Cancer Hospital and Solove Research Institute, Wexner Medical Center, The Ohio State University, Starling Loving Hall, B217, 320 West 10th Ave, Columbus, OH 43210, USA

Introduction

Salivary gland neoplasms are commonly encountered by head and neck surgeons and when malignant account for 8% of all head and neck cancers [1]. Most lesions occur in the parotid gland however cancer specifically of the sublingual gland (SLG) is quite rare and reported only in case reports and small series [2]. More specifically, SLG malignancy often occurs in the fifth decade of life and following appropriate treatment is typically well survived [3]. The overall 5-year survival has been reported at 68% with even improved rates seen in younger patients [3, 4]. Adenoid cystic carcinoma is the most common diagnosis yet many different pathologic etiologies have been reported [5].

In 1996, Ellis and Auclair classified an aggressive subtype of salivary gland cancer, undifferentiated carcinoma,

into three subtypes: lymphoepithelial carcinoma (LEC), small cell (undifferentiated) carcinoma (SCUC), and large cell undifferentiated carcinoma or simply large cell carcinoma (LCUC) [6]. This classification has been largely accepted in the literature and undifferentiated carcinoma remains a rare entity with sparse incidence in the SLG. Alternatively, NUT midline carcinoma (NMC) is another poorly differentiated or undifferentiated squamous carcinoma more recently recognized. It is an exceedingly rare disease with an unknown prevalence due to previous lack of available testing methods and poor clinical awareness. NMC can be a devastating disease and differentiation between these undifferentiated pathologies is critical as treatment plans are quite different.

We present an exemplary case of a NUT midline carcinoma of the sublingual gland in a young, otherwise healthy patient with an unforeseen clinical course. This patient's presentation, diagnosis and rapidly progressive nature of disease are uncharacteristic for salivary gland neoplasms but are typically the case in NMC.

Discussion

Clinical Case

A 26-year old male with no significant past medical history presented to the emergency department with 2 weeks of worsening right-sided oral cavity and submandibular neck pain, swelling, otalgia, and decreased oral intake unresponsive to oral antibiotics. The otolaryngology team was consulted and patient was found to have a full, indurated right floor of mouth with ipsilateral level I through III lymphadenopathy. A CT neck with contrast was obtained showing a 3.0×2.3 cm right oral cavity mass as well as multiple right submandibular and lateral chain necrotic lymph nodes (Fig. 1). The patient was taken to the operating room that night for incision and drainage due to concern for airway compromise. During surgery, a submucosal, granular tumor was encountered and biopsies were sent. Subsequent pathology revealed an undifferentiated carcinoma of the SLG.

Positron emission tomography (PET/CT) was obtained staging the disease as T2 N2b M0 (Fig. 2). The patient soon underwent resection of right floor of mouth, tongue, mandibular periosteum and supra-omohyoid contents with bilateral neck dissections. The oral cavity was reconstructed with a radial forearm fasciocutaneous free flap. Final pathologic staging of the disease was T4 N2c with 47 of 67 lymph nodes positive for carcinoma. The final pathology was reviewed by our head and neck pathologists and sent for outside consultation due to lack of typical staining patterns and appearance. The only diagnosis determined

Fig. 1 Pre-operative CT neck imaging. Axial computed tomography (CT) with contrast showing 3.0×2.3 cm right oral cavity mass with numerous ipsilateral enlarged, necrotic submandibular and lateral chain lymph nodes indicating stage IVA disease

pathologically could be high-grade undifferentiated or poorly differentiated carcinoma with squamous differentiation of the SLG (Fig. 3). However, the specimen was later submitted for molecular genetics post-mortem and the carcinoma was found to be positive for rearrangement of the *NUTM1* (15q14) locus with fusion of the *NUTM1* (15q14) and *BRD4* (19p13.12) loci, diagnostic for NMC.

The patient was referred for adjuvant chemoradiation however within just 2 weeks of surgery developed aggressive recurrent and metastatic disease. A PET/CT only 1 month after original imaging showed development of extensive lung and skeletal metastasis (Fig. 2). Dural metastatic disease was confirmed by MRI. The patient underwent palliative chemo-radiation with docetaxol and cisplatin (both 75 mg/m²) as well as palliative pain control but unfortunately passed away within just 4 months of initial presentation.

Assessment and Diagnosis

Neoplasms of the sublingual gland are rare and but most often malignant in 75% of cases. When any floor-of-mouth mass is identified a thorough history along with head and neck examination including dental exam are important to create a differential diagnosis. This is especially true in young patients where infectious, congenital, and benign masses are more common than malignancy.

In the setting of pain, as was the chief complaint in this case, an infectious etiology must certainly be considered; however a proper history can usually differentiate between patients with infection vs neoplasm. Regardless of the etiology, the primary management of a sublingual gland mass is almost exclusively surgical with pre-operative imaging and incisional or fine needle biopsy as indicated to clarify

Fig. 2 Pre and post-operative PET/CT imaging. Positron emission tomography (PET/CT) images before and after surgery. Image **a** shows several ipsilateral hypermetabolic cervical lymph nodes but no metastatic disease with lack of FDG-uptake (*bright areas*) elsewhere

in the body. Image **b** shows repeat PET/CT images 1 month after surgery revealing a rapid development of regional recurrence and extensive bony and axial skeleton metastatic lesions seen here in the humeral heads, clavicle, thoracic and lumbar spine, pelvis and femurs

Fig. 3 H&E staining of sublingual gland tumor. Hematoxylin and eosin staining of the primary lesion showing a hypercellular tumor with ovoid, monotonous cells without differentiation at low and high

power magnification. Focal squamous differentiation is a common feature as well in 80% of cases

a diagnosis. This case highlights the importance of sending any tissue for pathology during surgical intervention to confirm a diagnosis. The extent of resection is then determined by the pathology, anatomy, and location of the lesion. If malignancy is diagnosed, prompt management is important as a rich lymphatic network in this region creates an ideal environment for potential tumor spread. As in most cases, tumor size, grade, and histopathology are the key predictors of distant metastasis [7]. Overall survival is typically high with appropriate management.

This case, however, characterizes an unusually aggressive tumor of the SLG. The patient's clinical course was so vivid that the authors elected ongoing work-up after the patient's demise. Eventually the tumor was diagnosed as

NMC after identifying the pathognomonic gene rearrangement on FISH analysis.

NUT Midline Carcinoma

NMC is known to represent an aggressive malignancy defined as a poorly or undifferentiated carcinoma in a mid-line location. Most cases present in the thorax or mediastinum however one-third of cases occur in the head and neck [8]. These lesions arise from a single gene translocation creating the BRD-NUT fusion protein acting to block cellular differentiation and promote uncontrolled growth of tumor cells [9]. This particular balanced chromosomal translocation t(15;19) results in the BRD4-NUT oncogene

which bypasses the typical route of accumulated mutations on the way to squamous cell carcinoma. Diagnostic confirmation is typically made by confirming the presence of the *NUT* proto-oncogene translocation using FISH analysis [10]. Furthermore, immunohistochemical testing is now available using a monoclonal antibody to identify the BRD-NUT fusion protein with reported sensitivity and specificity of 87% and 100% respectively [11]. Unfortunately, despite treatment attempts, this disease has been shown to have rapid progression, hematogenous metastasis, and overall poor survival at a median of 6.7 months [12].

Recently, a single case of NMC was described in the SLG and it has been previously reported in other salivary tissue as well [10, 13, 14]. Due to its poorly differentiated nature and low clinical awareness however, this diagnosis is likely often missed. First, it requires clinical suspicion based on history, physical exam and pre-operative work-up. Then histopathologically, although no pathognomonic features exist, the tumor is identified by round to slightly ovoid, monotonous undifferentiated cells with focal squamous differentiation in 35–40% of its cases [12, 15, 16]. Lastly however, diagnostic confirmation requires proper immunohistochemical staining for the NUT protein typically performed by an outside facility.

In confirming the rare incidence of NMC of the SLG, a complete review of the literature was performed (Table 1) including forty-eight previous case reports or series regarding SLG cancer. Overall, there were 17 different diagnoses reported with a 1.3 male to female ratio. The mean age at diagnosis was 54 years and only 4.6% of cases were reported in patients 30 years of age or younger. In addition, a report of previously reviewed data from the SEER database from 1973 to 2004 found only three cases of SLG cancer in patients under the age of 30 years [4]. Reported treatment modalities, when described, are largely surgical with or without adjuvant therapy. Only three cases were treated primarily without surgery when lymphoma was excluded and two of these patients were over the age of 60 years.

Many different SLG histopathologic diagnoses are reported (Table 1). As expected, adenoid cystic carcinoma was most encountered in the literature (45%). Mucoepidermoid carcinoma was second most common (19%). Other diagnoses included adenocarcinoma, acinic cell, salivary duct, basal cell, clear cell and myoepithelial carcinoma, malignant pleomorphic adenoma, transformed carcinoma ex pleomorphic, as well as other less common lesions. Only one report of NMC exists to our knowledge [10].

Due to its midline location and difficult to interpret pathologic features, NMC can be misdiagnosed as salivary gland undifferentiated carcinoma although this too is uncommon in the SLG. Undifferentiated carcinoma has been reported in other major salivary glands but was not found in our review of the literature in the SLG [6]. By

definition, these tumors lack the histomorphologic features of squamous or glandular carcinoma as well as any other specific types of salivary gland neoplasia.

Undifferentiated Carcinoma

In order to more precisely define undifferentiated carcinoma, three subtypes have been described (Table 2): SCUC, LEC, LCUC. SCUC is neuroendocrine in nature and characterized by smaller cells with typical molding patterns on routine staining. It is an aggressive neoplasm and metastasis is always a consideration.

Lymphoepithelial carcinoma and LCUC both consist of large cells, but can usually be distinguished from one another pathologically and by clinical course. LEC is a tumor characterized by large epithelial cells within a dense lymphoid stroma [83]. EBV positivity is usually associated with this disease in endemic areas (i.e. southern China, Greenland, Alaska) but can occasionally be found in non-endemic areas [84, 85]. In the oropharynx, HPV has been found to associate with LEC as well [86]. Overall 5-year survival is quite good and reported as high as 86% for all ages [83]. Alternatively, LCUC and SCUC lacks any type of differentiation, although some cases have been described to show neuroendocrine features by immunohistochemistry or electron microscopy. It is a rare carcinoma which usually occurs in patients over the age of 60 years. Most involve the parotid gland, but minor salivary gland origin has also been reported [87].

Similarly, SCUC and LCUC have an aggressive behavior with poor overall prognosis. Locoregional disease is found in a majority of patients with up to 75% of cases diagnosed at stage 4. The overall 5-year survival is under 40% despite initiation of aggressive management [83]. To our knowledge, no cases of SCUC or LCUC have been previously described in the SLG but have been in larger salivary glands. Although the features of these diseases can be similar, with proper work-up and testing, a distinction can be made between these and NMC.

NMC Treatment Considerations

The one previous case of NMC described in the SLG and was found to have a similar biologic behavior to this case. This has also been true for other locations as well with an aggressive metastatic course and early demise despite lack of clear patient risk factors and aggressive treatment. Use of chemotherapy and radiation therapy have been reported with variable responses however outcomes remain poor [12]. Surgery remains a critical part of the treatment algorithm as aggressive upfront resection with negative margins is a significant predictor of overall survival despite adjuvant therapy [16]. Due to the nature of this disease however,

Table 1 All reported case reports of sublingual gland malignancies after literature review

Authors (year) [Ref]	Age (years)	Gender (#)	Pathology (#)	Treatment(s)
Andreasen et al. (2015) [10]	40	F	NUT carcinoma	
Hirvonen et al. (2015) [17]			ACC (2)	
Lawal et al. (2015) [18]			ACC, AcCA (2), AD NOS, PLGA	
Maruse et al. (2015) [19]	75	F	MEC w/ectopic bone	Surgery
Roy et al. (2015) [20]	55	M	LEC	Surgery, RT
Ban et al. (2014) [21]	44	F	LEC	
Leiser et al. (2014) [22]	19	F	LEC	Surgery
Mohanty et al. (2014) [23]	61	F	MEC	Surgery
Bradley et al. (2013) [24]			ACC (3), MEC (3)	
Eichhorn et al. (2013) [25]	56	F	ACC/SDC	Surgery, RT
Fang et al. (2013) [26]			ACC	
Gillenwater et al. (2013) [27]	80	M	ACC	RT
Kim et al. (2013) [28]	54	M	HCCC	Surgery, RT
Lawal et al. (2013) [29]			ACC, AD NOS, PLGA	
Adirajaiah et al. (2012) [30]	52	F	AD	Surgery, RT
Airyoshi et al. (2012) [31]	70	M	CexPa	Surgery
Lukšić et al. (2012) [32]			ACC (3), MEC (3), Cex PA	
Bombeccari et al. (2011) [33]	70	M	MEC	Surgery
Kumar et al. (2011) [34]	35	F	MEC	Surgery
López-Quile et al. (2011) [35]	43	F	HCCC	Surgery, RT
Zdanowski et al. (2011) [36]	37–68	M(8), F(4)	ACC (8), MED, SDC (2), PLGA	Surgery +/- RT
Gadre et al. (2009) [37]	54	F	MALT Lymphoma	RT
Papadogeorgakis et al. (2009) [38]	47	F	ACC	Surgery, RT
Weinreb et al. (2009) [39]	50	M	MEC	Surgery
Kwon et al. (2008) [40]	36	M	LAC	Surgery
Saito et al. (2008) [41]	73	M	ACC	Surgery
Yamada et al. (2007) [42]	67	M	AD	Surgery, CT
Yu et al. (2007) [43]	24–75	M(16), F(13)	ACC (18), MED (5), AD (3), PLGA, Mal PA	Many
Maruya et al. (2006) [44]	51	M	ACC	Surgery, RT, CT
Da Crus Perez et al. (2005) [45]	16–70	M(2), F(4)	ACC (4), MEC (2)	Surgery +/- RT
Gurney et al. (2005) [46]			ACC (2)	Surgery, RT
Matsuzaka et al. (2004) [47]	42	M	AcCA	Surgery
Shigematsu et al. (2004) [48]	59	F	ACC	Surgery, RT
Ogawa et al. (2003) [49]	59	M	SFT	Surgery
Ota et al. (2001) [50]	79	M	AcCA	Surgery
Ma'aita et al. 1999 [51]			ACC	
Blanchaert et al. (1998) [52]	81	F	PLGA	Surgery
Foss et al. (1997) [53]			AD (2)	
Krogdahl et al. (1997) [54]	63	M	AD	Surgery, RT
McFall et al. (1997) [55]	16	F	ACC	
Sakashita et al. (1997) [56]	56	M	AD NOS	Surgery
Mima et al. (1996) [57]	76	M	BCC	Surgery
Whear et al. (1993) [58]	57	F	ACC	Surgery
Williams et al. (1993) [59]	74	M	Lymphoma	Surgery
Danford et al. (1992) [60]	38	M	AD	Surgery
Anderson et al. (1991) [5]			ACC (3), CexPA (2), AD	
Uchimaya et al. (1991) [61]	27	M	AD	Surgery
Hamper et al. (1989) [62]			AD	
Shwartz-Arad et al. (1987) [63]	72	M	Lymphoma	Surgery, RT
Anonsen et al. (1985) [64]	76	M	CS	Surgery

Table 1 (continued)

Authors (year) [Ref]	Age (years)	Gender (#)	Pathology (#)	Treatment(s)
Nishijima et al. (1984) [65]	55	M	AD	Surgery
van den Akker et al. (1981) [66]	53	F	AcCa	Surgery
Shidnia et al. (1980) [67]			ACC, MEC, AD (2), other carcinoma	
Spiro et al. (1977) [68]			Malignant mixed tumor	
Glanzmann et al. (1976) [69]			ACC	
Main et al. (1976) [70]	46–75	M(1), F(2)	ACC, MEC, AcCA	
Washizu et al. (1975) [71]			ACC (2)	
Ito et al. (1974) [72]	68	F	ACC	
Ramsden et al. (1973) [73]			ACC	
Furuichi et al. (1972) [74]	51	M	Malignant mixed tumor	
Rankow et al. (1969) [75]	41–73	M(3), F(4)	ACC (4), MEC (3)	Surgery +/- RT
Suzuki et al. (1968) [76]	45	M	AcCA	
Rosenfeld et al. (1966) [77]			ACC, MEC, Mal mixed, unclassified carcinoma	
Smith et al. (1966) [78]			ACC	Surgery
Luccioli et al. (1965) [79]	49	F	MEC	
Gore et al. (1964) [80]			MEC (3)	
Badini et al. (1962) [81]			ACC	
Grage et al. (1962) [82]			ACC	

AcCA acinic cell carcinoma, ACC adenoid cystic carcinoma, AD adenocarcinoma, AD NOS adenocarcinoma not otherwise specified, BCC basal cell carcinoma, CexPA carcinoma ex pleomorphic adenoma, CS carcinosarcoma, EMC Epithelial-myoepithelial carcinoma, HCCC hyaline clear cell carcinoma, LAC lymphadenomatous carcinoma, LEC lymphoepithelial carcinoma, MEC mucoepidermoid carcinoma, PA pleomorphic adenoma, PLGA polymorphous low grade adenocarcinoma, SDC salivary duct carcinoma, SFT solitary fibrous tumor, CT chemotherapy, RT radiation therapy

Table 2 Comparison of undifferentiated carcinoma subtype characteristics

Diagnosis	Distinctive characteristics	Immunohistochemical findings
NUT midline carcinoma	Monotonous cells with focal squamous differentiation (80%) BRD-NUT oncogene pathognomonic Rapidly progressive disease with poor survival; median 6.7 months	Positive cytokeratins, NUT protein, p63
Lymphoepithelial carcinoma	Large epithelial cells in dense lymphoid stroma EBV-associated 5-year survival greater than 86%	Positive cytokeratins and EBER
Large cell undifferentiated carcinoma	Large undifferentiated cells, neuroendocrine features Typically patients older than 60 years of age 5-year survival <40%; typically diagnosed at advanced stage	Positive synaptophysin, chromogranin, NSE (neuron specific enolase), CD56, CD57, cytokeratins
Small cell undifferentiated carcinoma	Small undifferentiated cells, 1 neuroendocrine features 5-year survival <40%; typically diagnosed at advanced stage	Positive synaptophysin, chromogranin, NSE (neuron specific enolase), CD56, CD57, cytokeratins

cure is rare despite an appropriate oncologic resection. Therefore, testing for NMC in patients with similar clinical presentation of a midline, undifferentiated lesion may alter the treatment course. It is essential to test for NMC in this setting in order to provide appropriate pre-operative counseling and consider alternative options including referral for clinical trial enrollment.

As discussed, the oncologic mechanism behind NMC is the function of the BRD4-NUT protein allowing ongoing proliferation and preventing cellular differentiation.

This is confirmed by siRNA knock out of the BRD4-NUT oncoprotein however further details of the downstream biologic mechanisms at play remain largely unknown [8]. BRD4 is a known member of the dual bromodomain protein family (BET) that functionally binds acetylated chromatin at these bromodomains [88]. As such, acetyl-histone mimics (BETi) can interfere with this domain interaction and has the ability to inhibit the function of the BRD4-NUT protein allowing cellular differentiation to proceed [89]. Novel BETi targeted therapeutics are

now being investigated in early clinical trials currently enrolling patients.

Furthermore, the BRD4-NUT protein is known to bind and activate histone acetyl-transferase p300, hypothesized to acetylate chromatin and create a feed-forward mechanism leading to neoplasia [90]. Histone deacetylase inhibitors artificially increase acetylation leading to BRD4-NUT function reversal and thus a return to regular cellular progression. The use of histone deacetylase inhibitors have shown clinical response in both in-vitro and animal models and more recently, pediatric patients have been treated with histone deacetylase-containing regimens with promising early clinical results [91].

Conclusion

When managing any floor-of-mouth lesion, one should always keep a high level of suspicion for malignancy regardless of patient's age, demographics, or risk factors. In the setting of a midline lesion with poor or undifferentiated features, especially with focal squamous differentiation, NMC must be considered and we recommend sending genetic testing or immunohistochemical staining for the NUT proto-oncogene. Further knowledge of this disease will improve diagnosis, more accurately define incidence, allow physicians to properly counsel on treatment options, and help identify patients for clinical trial enrollment for much needed prospective evaluation of treatment modalities.

Funding There was no external funding for this project.

Compliance with Ethical Standards

Conflict of interest Nolan Seim declares that he has no conflict of interest. Ramez Phillips declares he has no conflict of interest. Lynn Schoenfield declares that she has no conflict of interest. Theodoros Teknos declares that he has no conflict of interest. James Rocco declares that he has no conflict of interest. Amit Agrawal declares that he has no conflict of interest. Enver Ozer declares that he has no conflict of interest. Ricardo Carrau declares that he has no conflict of interest. Stephen Kang declares that he has no conflict of interest. Matthew Old declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not indicated for this study.

References

- Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer*. 2005;114(5):806–816.
- Spiro RH, Armstrong J, Harrison L, Geller NL, Lin S-Y, Strong EW. Carcinoma of major salivary glands. Recent trends. *Arch Otolaryngol Head Neck Surg*. 1989;115:316–332.
- Lee RJ, Tong EL, Patel R, Satyadev N, Christensen RE. Malignant sublingual gland tumors: demographics, prognostic factors, and treatment outcomes. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;121(2):180–187.
- Rutt AL, Hawkshaw MJ, Lurie D, Sataloff RT. Salivary gland cancer in patients younger than 30 years. *Ear Nose Throat J*. 2011;90(4):174–184.
- Andersen LJ, Therkildsen MH, Ockelmann HH, Bentzen JD, Schiødt T, Hansen HS. Malignant epithelial tumors in the minor salivary glands, the submandibular gland, and the sublingual gland. Prognostic factors and treatment results. *Cancer*. 1991;68(11):2431–2437.
- Ellis GL, Auclair PL. Tumors of the salivary glands (series 4). Washington, DC: Armed Forces Institute of Pathology; 2008.
- Jegadeesh NN. Outcomes and prognostic factors in modern era management of major salivary gland cancer. *Oral Oncol*. 2015;51(8):770–777.
- French CA. The Importance of diagnosing NUT midline carcinoma. *Head Neck Pathol*. 2013;7(1):11–16.
- French CA, Miyoshi I, Kubonishi I, et al. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. *Cancer Res*. 2003;63:304–307.
- Andreasen S, French CA, Josiassen M, Hahn CH, Kiss K. NUT carcinoma of the sublingual gland. *Head and Neck Pathol*. 2016;10(3):362–366.
- Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. *Am J Surg Pathol*. 2009;33:984–991.
- Bauer D, Mitchell C, Strait K, et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. *Clin Cancer Res*. 2012;18:5773–5779.
- den Bakker MA, Beverloo BH, van den Heuvel-Eibrink MM, et al. NUT midline carcinoma of the parotid gland with mesenchymal differentiation. *Am J Surg Pathol*. 2009;33:1253–1258.
- Ziai J, French CA, Zambrano E. NUT gene rearrangement in a poorly-differentiated carcinoma of the submandibular gland. *Head Neck Pathol*. 2010;4:163–168.
- Wartchow EP, Moore TS, French CA, et al. Ultrastructural features of NUT midline carcinoma. *Ultrastruct Pathol*. 2012;36:280–284.
- Chau NG, Hurwitz S, Mitchell CM, et al. Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck. *Cancer*. 2016;122(23):3632–3640.
- Hirvonen K, Back L, Saarilahti K, Leivo I, Hagstrom J, Makitie AA. Pattern of recurrent disease in major salivary gland adenocystic carcinoma. *Virchows Arch*. 2015;467:19–25.
- Lawal AO, Adisa AO, Kolude B, Adeyemi BF. Malignant salivary gland tumours of the head and neck region: a single institutions review. *Pan Afr Med J*. 2015;20:121.
- Maruse Y, Kawano S, Kiyoshima T, Goto Y, Matsubara R, Chikui T, Yoshiga D, Nakamura S. Case of mucoepidermoid carcinoma of the sublingual gland accompanied with extensive dystrophic calcification and intratumoral bone formation. *Head Neck*. 2015;37(11):E161–E164.
- Roy L, Moubayed S, Ayad T. Lymphoepithelial carcinoma of the sublingual gland: case report and review of literature. *J Oral Maxillofac Surg*. 2015;(73(9):1878.e1–5.
- Ban X, Wu J, Mo Y, et al. Lymphoepithelial carcinoma of the salivary gland: morphologic patterns and imaging features on CT and MRI. *AJNR Am J Neuroradiol*. 2014;35(9):1813–1819.

22. Leiser Y, Peled M, Wolff A, El-Naaj IA. Lymphoepithelial carcinoma: review of the treatment modalities and report of a rare case in the sublingual gland. *J Oral Maxillofac Surg.* 2014;72(4):828–828.
23. Mohanty S, Pathak H. Epithelial-myoepithelial carcinoma of floor of mouth: A case report with cytological, histological and immunohistochemical correlation. *Natl J Maxillofac Surg.* 2014;5(2):195–197.
24. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. *Br J Oral Maxillofac Surg.* 2013;51(5):399–403.
25. Eichhorn W, Precht C, Wehrmann M, et al. First description of a hybrid tumor of the sublingual gland. *Anticancer Res.* 2013;33(10):4567–4571.
26. Fang QG, Shuang S, Li ZN, Zhang X, Liu FY, Sun CF. Epithelial salivary gland tumors in children: a twenty-five-year experience of 122 patients. *Int J Pediatr Otorhinolaryngol.* 2013;77(8):1252–1254.
27. Gillenwater AM, Frank SJ, Fatani H, El-Naggar AK. Primary intestinal-like adenocarcinoma of major salivary glands: 2 instances of previously undocumented phenotype. *Head Neck.* 2013;35(8):234–236.
28. Kim DW, Park HJ, Cha IH, Yang DH, Kim HS, Nam W. An atypical case of rare salivary malignancy, hyalinizing clear cell carcinoma. *J Korean Assoc Oral Maxillofac Surg.* 2013;39:283–288.
29. Lawal AO, Adisa AO, Kolude B, Adeyemi BF, Olajide MA. A review of 413 salivary gland tumours in the head and neck region. *J Clin Exp Dent.* 2013;5(5):e218–222.
30. Adirajaiah S, Anehosur V, Sumana, Gopalakrishnan K. Adenocarcinoma of the sublingual salivary gland: a case report. *J Oral Biol Craniofac Res.* 2012;2(3):206–209.
31. Ariyoshi Y, Shimahara M, Konda T, Tsuji M. Carcinoma ex pleomorphic adenoma of the sublingual gland: a case report. *Int J Oral Sci.* 2012;4(1):50–53.
32. Lukšić I, Virag M, Manojlović S, Macan D. Salivary gland tumours: 25 years of experience from a single institution in Croatia. *J Craniomaxillofac Surg.* 2012;40(3):e75–e81.
33. Bombeccari GP, Guzzi GP, Pallotti F, Spadari F. Mucoepidermoid carcinoma of the sublingual gland associated with Sjögren's syndrome. *Indian J Cancer.* 2011;48:381–383.
34. Kumar AN, Nair PP, Thomas S, Raman PS, Bhambal A. Mucoepidermoid carcinoma of sublingual gland: a malignant neoplasm in an uncommon region. *BMJ Case Rep.* 2011;12:2011.
35. López-Quiles J, Ferreira E, Jiménez-Heffernan JA, Del Canto M. Clear cell carcinoma of the major salivary glands in an HIV-infected patient. *Int J Oral Maxillofac Surg.* 2011;40(7):760–763.
36. Zdanowski RR. Sublingual gland tumors: clinical, pathologic, and therapeutic analysis of 13 patients treated in a single institution. *Head Neck.* 2011;33(4):476–481.
37. Gadre S, Ryan MW, Logroño R. MALT lymphoma of the floor of the mouth: a case report. *Ear Nose Throat J.* 2009;88(8):E1–E3.
38. Papadogeorgakis N, Kalfarentzos EF, Vourlakou C, Malta F, Exarhos D. Simultaneous pleomorphic adenoma of the left parotid gland and adenoid cystic carcinoma of the contralateral sublingual salivary gland: a case report. *Oral Maxillofac Surg.* 2009;13(4):221–224.
39. Weinreb I, Seethala RR, Perez-Ordoñez B, Chetty R, Hoschar AP, Hunt JL. Oncocytic mucoepidermoid carcinoma: clinicopathologic description in a series of 12 cases. *Am J Surg Pathol.* 2009;33(3):409–416.
40. Kwon YD, Biesterfeld S, Hansen T, Schwerdtfeger A, Kunzel M. Lymphadenomatous carcinoma of the sublingual gland: report of a first case in an unusual localization. *Head Neck.* 2008;30(10):1394–1398.
41. Saito M, Nishiyama H, Maruyama S, Oda Y, Saku T, Hayashi T. Adenoid cystic carcinoma of sublingual gland involving the submandibular duct. *Dentomaxillofac Radiol.* 2008;37(7):421–424.
42. Yamada S, Matsuo T, Baba N, Rokutanda S, Kawasaki G, Mizuno A, Fujita S. High-grade papillary cystadenocarcinoma of the sublingual gland: a case report. *J Oral Maxillofac Surg.* 2007;65(6):1223–1227.
43. Yu T, Gao QH, Wang XY, Wen YM, Li LJ. Malignant sublingual gland tumors: a retrospective clinicopathologic study of 28 cases. *Int Soc Cell.* 2007;72(1–2):39–44.
44. Maruya S, Namba A, Matsubara A, et al. Salivary gland carcinoma treated with concomitant chemoradiation with intraarterial cisplatin and docetaxel. *Int J Clin Oncol.* 2006;11(5):403–406.
45. da Cruz Perez DE, Pires FR, Alves FA, Almeida OP, Kowalski LP. Sublingual salivary gland tumors: clinicopathologic study of six cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;100:449–453.
46. Gurney TA, Eisele DW, Weinberg V, Shin E, Lee N. Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. *Laryngoscope.* 2005;115(7):1278–1282.
47. Matsuzaka K, Shibahara T, Murakami S, Lee DH, Shimono M, Inoue T. Acinic cell carcinoma found by recurrence of a mucous cyst in the sublingual gland. *Bull Tokyo Dent Coll.* 2004;45(2):95–98.
48. Shigematsu H, Magoshi S, Suzuki S, Kusama K, Sakashita H. An apparent radiation-induced carcinoma of the parotid gland following treatment for adenoid cystic carcinoma of the sublingual gland: a case report. *J Oral Maxillofac Surg.* 2004;62(9):1169–1174.
49. Ogawa I, Sato S, Kudo Y, Miyauchi M, Sugiyama M, Suei Y, Takata T. Solitary fibrous tumor with malignant potential arising in sublingual gland. *Pathol Int.* 2003;53(1):40–45.
50. Ota Y, Arai I, Aoki T, Yamazaki H, Karakida K, Tsukinoki K. Acinic cell carcinoma of the sublingual gland accompanied by bone formation. *Tokai J Exp Clin Med.* 2001;26(4–6):127–130.
51. Ma'aitha JK, Al-Kaisi N, Al-Tamimi S, Wraikat A. Salivary gland tumors in Jordan: a retrospective study of 221 patients. *Croat Med J.* 1999;40(4):539–542.
52. Blanchaert RH, Ord RA, Kumar D. Polymorphous low-grade adenocarcinoma of the sublingual gland. *Int J Oral Maxillofac Surg.* 1998;27(2):115–117.
53. Foss RD, Ellis GL, Auclair PL. Salivary gland cystadenocarcinomas. A clinicopathologic study of 57 cases. *Am J Surg Pathol.* 1996;20(12):1440–1447.
54. Krogdahl AS, Schou C. Mucinous adenocarcinoma of the sublingual gland. *J Oral Pathol Med.* 1997;26(4):198–200.
55. McFall MR, Irvine GH, Eveson JW. Adenoid cystic carcinoma of the sublingual salivary gland in a 16-year-old female—report of a case and review of the literature. *J Laryngol Otol.* 1997;111(5):485–488.
56. Sakashita H, Miyata M, Miyamoto H, Minato H. Adenocarcinoma originating in the sublingual gland: report of a case. *J Oral Maxillofac Surg.* 1997;55(7):764–767.
57. Mima T, Shirasuna K, Kishino M, Matsuya T. Basal cell adenocarcinoma of the sublingual gland: report of a case. *J Oral Maxillofac Surg.* 1996;54(9):1121–1123.
58. Whear NM, Addy JM. Adenoid cystic carcinoma of the sublingual gland—an unusual presentation. *Br J Oral Maxillofac Surg.* 1993;31(2):113–116.
59. Williams TP, Vincent SD, Connor FA Jr. A mass in the floor of the mouth. *J Oral Maxillofac Surg.* 1993;51(12):1385–1388.
60. Danford M, Eveson JW, Flood TR. Papillary cystadenocarcinoma of the sublingual gland presenting as a ranula. *Br J Oral Maxillofac Surg.* 1992;30(4):270–272.

61. Uchiyama K, Ikeuchi S, Shiba H, Okada Y, Asanami S. Adenocarcinoma of the sublingual gland. *Keio J Med*. 1991;40(1):20–24.
62. Hamper K, Brüggmann M, Caselitz J, et al. Prognosis of salivary adenocarcinomas. A retrospective study of 52 cases with special regard to cytochemically assessed nuclear DNA content. *Virchows Arch A Pathol Anat Histopathol*. 1989;416(1):57–64.
63. Schwartz-Arad D, Azaz B, Shteyer A. Malignant lymphoma arising in the submandibular and sublingual salivary glands: report of cases. *J Oral Maxillofac Surg*. 1987;45(9):795–799.
64. Anonsen C, Dobie RA, Hoekema D, Huang TW, Gown AM. Carcinosarcoma of the floor of mouth. *J Otolaryngol*. 1985;14(4):215–220.
65. Nishijima W, Tokita N, Takooda S, Tsuchiya S, Watanabe I. Adenocarcinoma of the sublingual gland: case report and 50 year review of the literature. *Laryngoscope*. 1984;94(1):96–101.
66. van den Akker HP, Busemann-Sokole E, Becker AE. Acinic cell carcinoma of the sublingual gland. Scintigraphy in pre-operative evaluation. *Int J Oral Surg*. 1981;10(5):363–366.
67. Shidnia H, Hornback NB, Hamaker R, Lingeman R. Carcinoma of major salivary glands. *Cancer*. 1980;45(4):693–697.
68. Spiro RH, Huvos AG, Strong EW. Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases. *Cancer*. 1977;39(2):388–396.
69. Glanzmann C, Aberle HG, Burgener F, Willi F, Horst W. Radiotherapy of salivary gland carcinomas (results from 80 patients). *Strahlentherapie*. 1976;152(5):395–403.
70. Main JH, Orr JA, McGurk FM, McComb RJ, Mock D. Salivary gland tumors: review of 643 cases. *J Oral Pathol*. 1976;5(2):88–102.
71. Washizu K. Salivary Gland Tumors. In: Takeda C, Nakahara K, editors. *Toukeibu Shuyo Zufu*. Tokyo: Nakayama-Shoten; 1996. p. 231–233.
72. Ito T. Adenoid cystic carcinoma of the left sublingual gland. *Jpn J Oral Surg*. 1974;20:315.
73. Ramsden D, Sheridan BF, Newton NC, De Wilde FW. Adenoid cystic carcinoma of the head and neck: a report of 30 cases. *Aust N Z J Surg*. 1973;43(2):102–108.
74. Furuichi N, et al. A malignant mixed tumor of the sublingual gland. *Otolaryngology*. 1972;44:41–45.
75. Rankow RM, Mignogna F. Cancer of the sublingual salivary gland. *Am J Surg*. 1969;118(5):790–795.
76. Suzuki H, Henderson R. Acinic cell carcinoma of the sublingual gland. *Arch Otolaryngol*. 1968;87(2):146–149.
77. Rosenfeld L, Sessions DG, McSwain B, Graves H Jr. Malignant tumors of salivary gland origin: 37-year review of 184 cases. *Ann Surg*. 1966;163(5):726–735.
78. Smith LC, Lane N, Rankow RM. Cylindroma (adenoid cystic carcinoma). A report of fifty-eight cases. *Am J Surg*. 1965;110(4):519–526.
79. Luccioli GM, Clement H, Palmer JD. An analysis of 50 carcinomas of the salivary glands. *Can J Surg*. 1965;8(4):389–399.
80. Gore DO, Annamunthodo H, Harland A. Tumors of salivary gland origin. *Surg Gynecol Obstet*. 1964;119:1290–1296.
81. Bandini A, La Maccia E. Cylindroma of the sublingual gland. *Riforma Med*. 1962;76:889–892.
82. Grage TB, Lober PH. Malignant tumors of the major salivary glands. *Surgery*. 1962;52:284–294.
83. Wang CP, Chang YL, Ko JY, et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. *Cancer*. 2004;101:2020–2027.
84. Manganaris A, Patakiouta F, Xirou P, Manganaris T. Lymphoepithelial carcinoma of the parotid gland: is an association with Epstein-Barr virus possible in non-endemic areas? *Int J Oral Maxillofac Surg*. 2007;36:556–559.
85. Hamilton-Dutoit SJ, Therkildsen MH, Nielsen NG, et al. Undifferentiated carcinoma of the salivary gland in Greenlandic Eskimos: demonstration of Epstein-Barr virus DNA in situ hybridization. *Hum Pathol*. 1991;22:811–815.
86. Singhi AD, Stelow EB, Mills SE, Westra WH. Lymphoepithelial-like carcinoma of the oropharynx, a morphologic variant of HPV-related head and neck carcinoma. *Am J Surg Pathol*. 2010;34:800–805.
87. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press; 2005. p. 200–249.
88. French CA, Ramirez CL, Kolmakova J, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. *Oncogene*. 2008;27:2237–2242.
89. Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. *Nature*. 2010;468:1067–1073.
90. Reynoird N, Schwartz BE, Delvecchio M, et al. Oncogenesis by sequestration of CBP/p300 in transcriptionally inactive hyperacetylated chromatin domains. *EMBO J*. 2010;29:2943–2952.
91. Schwartz BE, Hofer MD, Lemieux ME, et al. Differentiation of NUT midline carcinoma by epigenomic reprogramming. *Cancer Res*. 2011;71:2686–2696.