Recent Developments in Salivary Gland Pathology

Prof. Alena Skálová, MD, PhD
Charles University, Faculty of Medicine, Plzen, Czech Republic

21st National Congress of Pathology, İzmir, 16 - 20 November 2011
Update on molecular diagnostics of salivary gland tumors

Newly recognized entities

Known tumor entities with new findings
Update on molecular diagnostics of salivary gland tumors
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- NUT midline carcinoma
- Mammary analogue secretory carcinoma (MASC)
Mucoepidermoid carcinoma

- common malignant SG tumor
- broad age range, minor and major SG
- translocation $t(11;19)$ specific for MEC
- $MECT1$-$MAML2$ translocation
- FISH or RT-PCR analysis
Mucoepidermoid carcinoma

- Highly variable clinical prognosis
- Grading systems - AFIP, Brandwein
- Translocation $t(11;19)$ fuses **MECT1** (**mucoepidermoid carcinoma translocated-1**) at 19p13 with **MAML2** (**mastermind-like gene family**) at 11q21
- Fusion positive patients have better outcomes
  - Less local recurrences, metastases and tumor-related deaths
Fusion positive cases of MEC have better outcome even in high grade morphology.
MECT1-MAML2 translocation can be used in differential dg.

Oncocytic Mucoepidermoid Carcinoma
Clinicopathologic Description in a Series of 12 Cases

Ilan Weinreb, MD,* Raja R. Seethala, MD,† Bayardo Perez-Ordoñez, MD,* Runjan Chetty, MD,* Aaron P. Hoschar, MD,‡ and Jennifer L. Hunt, MD‡

Adenoid cystic carcinoma

- both minor and major SG
- relentless clinical course with late recurrences and distant metastases
- c-KIT (CD117) over-expression
- No evidence of *c-KIT* gene mutations
  - Mixed results with imatinib which targets c-kit
Adenoid cystic carcinoma

- Recurrent \( t(6;9) \) translocation in AdCC of both head and neck (salivary, lacrimal, ceruminal glands) and breast
- Translocation fuses \( MYB \) oncogene with transcription factor gene \( NFIB \)
  - Leads to chimeric \( MYB-NFIB \) fusion transcript
  - \( MYB-NFIB \) fusion is a candidate therapeutic target
  - MYB activation through gene fusion is a major oncogenic event in AdCCa of many sites
NUT Midline Carcinoma

- New type of aggressive ca has been described, \( t(15;19)(q14;p13.1) \)
- Midline structures of head and neck in young adults
- Composed of undifferentiated basaloid cells with focal squamous differentiation

- Dual color FISH analysis for NUT gene with splitting of green-red probe on tu cells
- \( BRD4 \) dual color FISH analysis
NUT ca

Parotid gland in 15-y old male

CAM 5.2+
CD56+
p63+
Newly recognized entities

- Mammary analogue secretory carcinoma
- Sclerosing polycystic adenosis
- Cribriform adenocarcinoma, tongue type
- Keratocystoma

WHO 2005
Mammary Analogue Secretory Carcinoma of Salivary Glands, Containing the ETV6-NTRK3 Fusion Gene: A Hitherto Undescribed Salivary Gland Tumor Entity

Alena Skálová, MD, PhD,* † Tomas Vanecek, PhD, † Radek Sima, MSc, † Jan Laco, MD, §
Ilan Weinreb, MD, ‖ Bayardo Perez-Ordonez, MD, FRCPC, ‖ Ivo Starek, MD, PhD, ‟
Marie Geierova, MD, † Roderrick HW. Simpson, MD, ** Fabricio Passador-Santos, MD, † †
Ales Ryska, MD, PhD, § Ilmo Leivo, MD, † † Zdenek Kinkor, MD, PhD, † and Michal Michal, MD*

Abstract: We present a series of 16 salivary gland tumors with histomorphologic and immunohistochemical features reminiscent of secretory carcinoma of the breast. This is a hitherto undescribed and distinctive salivary gland neoplasm, with features resembling both salivary acinic cell carcinoma (AciCC) and low-grade cystadenocarcinoma, and displaying strong similarities to breast secretory carcinoma. Microscopically, the tumors have a lobulated growth pattern and are composed of microcystic and glandular spaces with abundant eosinophilic homogenous or bubbly secretory material positive for periodic acid-Schiff, mucicarmine, MUC1, MUC4, and mammaglobin. The neoplasms also show strong vimentin, S-100 protein, and STAT5a positivity. For this tumor, we propose a designation mammary analogue secretory carcinoma of salivary glands (MASC). The 16 patients comprised 9 men and 7 women, with a mean age of 46 years (range 21 to 75). Thirteen cases occurred in the parotid gland, and one each in the minor salivary glands of the buccal mucosa, upper lip, and palate. The mean size of the tumors was 2.1 cm (range 0.7 to 5.5 cm). The duration of symptoms was recorded in 11 cases and ranged from 2 months to 30 years. Clinical follow-up was available in 13 cases, and ranged from 3 months to 10 years. Four patients suffered local recurrences. Two patients died, 1 of them owing to multiple local recurrences with extension to the temporal bone, and another owing to metastatic dissemination to cervical lymph nodes, pleura, pericardium, and lungs. We have shown a t(12;15) (p13;q25) ETV6-NTRK3 translocation in all but one case of MASC suitable for analysis. One case was not analyzable and another was not available for testing. This translocation was not found in any conventional salivary AciCC (12 cases), nor in other tumor types including pleomorphic adenoma (1 case) and low-grade cribriform cystadenocarcinoma (1 case), whereas ETV6-NTRK3 gene rearrangements were proven in all 3 tested cases of mammary secretory carcinoma. Thus, our results strongly support the concept that MASC and AciCC are different entities.

Key Words: salivary gland, acinic cell carcinoma, secretory carcinoma, mammary type, molecular pathology, ETV6-NTRK3 translocation

Mammary analogue secretory carcinoma of salivary glands
Secretory ca breast

MASC

Secretory ca breast
Secretory ca of breast

MASC
Secretory carcinoma of the breast containing the ETV6-NTRK3 fusion gene in a male: case report and review of the literature

C Arce*, D Cortes-Padilla1, DG Huntsman5, MA Miller6, A Dueñas-Gonzalez4, A Alvarado1, V Pérez3, D Gallardo-Rincón1 and F Lara-Medina1

Address: 1Division of Internal Medicine, Instituto Nacional de Cancerología, Mexico, 2Division of Clinical Research, Instituto Nacional de Cancerología, Mexico, 3Division of Pathology, Instituto Nacional de Cancerología, Mexico, 4Unidad de Investigacion Biomédica en Cancer, Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico e Instituto Nacional de Cancerología, Mexico, 5Genetic Pathology Evaluation Center of the Departments of Pathology, British Columbia Cancer Agency Vancouver Canada and 6General Hospital and University of British Columbia and the Prostate Centre at the Vancouver General Hospital, Vancouver, British Columbia, Canada

Email: C Arce* - haydeearce@hotmail.com; D Cortes-Padilla - dcortespadilla@yahoo.com; DG Huntsman - dhuntsman@bccancer.bc.ca; MA Miller - mmiller@bccancer.bc.ca; A Dueñas-Gonzalez - aduenas@incan.edu.mx; A Alvarado - alberalvarm@gmail.com; V Pérez - vperaza@incan.edu.mx; D Gallardo-Rincón - gnaturaleza@prodigy.net; F Lara-Medina - fulises@lara.com

* Corresponding author

Published: 17 June 2005
Received: 22 March 2005
Accepted: 17 June 2005


This article is available from: http://www.wjso.com/content/3/1/35

-secretory carcinoma of breast is associated with t(12;15) (p13;q25) ETV6-NTRK3 translocation
-fusion gene first recognized in congenital fibrosarcoma
-in mammary lesions relatively specific for SC
Expression of ETV6-NTRK3 fusion transcript in the MASC and breast positive controls by RT-PCR. 1-16: Cases of MASC, PK-positive amplification control, NK-negative amplification control, H₂O – water. Arrows show translocation breakpoint.
**FISH analysis** using LSI ETV6 (TEL) (12p13) Dual Color, Break Apart Rearrangement Probe (VYSIS/Abbott). Green and red arrows show split signals indicating break of ETV6 gene. Yellow arrows show nonaltered chromosome.

No break of ETV6 gene in 14 salivary gland tu with secretory-like morphology
MASC

- distinctive salivary gland tumor (S100+) resembling breast secretory carcinoma
- ETV6-NTRK3 gene rearrangements demonstrated in MASC, not in AciCC
- MASC and salivary AciCC are distinct entities and should be recorded separately in salivary gland tumor classifications
Sclerosing polycystic adenosis

With recent molecular evidence supporting its neoplastic nature
Sclerosing Polycystic Adenosis

- is rare distinctive neoplastic lesion of the major salivary glands
- lesion resembles FCD/adenosis tumor of breast
- originally considered a sclerosing inflammatory pseudoneoplastic process
- it represents a true neoplastic condition characterized by clonality, focal dysplasia, and a tendency to recur
Sclerosing polycystic adenosis
Sclerosing polycystic adenosis
Sclerosing polycystic adenosis
Sclerosing polycystic adenosis
Variable degrees of hyperplasia and dysplasia
Clonal Nature of Sclerosing Polycystic Adenosis of Salivary Glands Demonstrated by Using the Polymorphism of the Human Androgen Receptor (HUMARA) Locus as a Marker

Alena Skálová, MD,* Douglas R. Gnepp, MD,† Roderick H. W. Simpson, MB CHB, FRCPath,‡ Jean E. Lewis, MD,§ Dirk Janssen, MD,¶ Radek Sima, MSc,** Tomas Vaněcek, MSc,** Silvana Di Palma, MD,†† and Michal Michal, MD*

Abstract: Sclerosing polycystic adenosis (SPA) is a recently described, rare lesion of the salivary glands that bears a resemblance to epithelial proliferative lesions of the breast. The true nature of the lesion is unknown, but to date it has been generally believed to represent a pseudoneoplastic sclerosis and inflammatory process. However, local recurrence developed in about one-third of the cases. Superimposed dysplastic changes ranging from low-grade dysplasia to carcinoma in situ were described in SPA. Although no metastases-related and/or disease-related patient deaths were documented, these clinical and histopathologic features raise the possibility that SPA might represent a neoplastic lesion. Polymorphism of the human androgen receptor locus is most frequently used to assess whether the pattern of X-chromosome inactivation is random or nonrandom, the latter strongly indicating clonality. In this study, the assay was applied to tissue from 12 examples of SPA. Three cases (males) were noninformative and 3 cases (females) could not be analyzed owing to poor quality of DNA, but all the remaining 6 lesions satisfied the criteria for monoclonality. We therefore conclude that the findings in the present study are further supporting evidence that SPA is a neoplasm, and not just a reactive process.

Key Words: sclerosing polycystic adenosis, salivary gland, clonality, HUMARA, dysplasia


Clonality by HUMARA
spectrum of dysplastic changes ranging to DCIS recurrences in 29% of cases
no meta, none died of disease

- Digestion of genomic DNA with methylation sensitive enzymes
- PCR amplification of CAG repeats at HUMARA locus at chromosome X
Cribriform adenocarcinoma of tongue CAT
Cribiform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue

M Michal, A Skálová, R H W Simpson, W F Raslan, R Čuřík, I Leivo & P Mukenšnábl

Department of Pathology, Medical Faculty of Charles University in Pilsen, Pilsen, Czech Republic; Department of Pathology, Postgraduate Medical School, University of Exeter, UK; Department of Pathology, ARAMCO Medical Services, Dhahran, Saudi Arabia; Department of Pathology, Ostrava Faculty Hospital, Czech Republic; and Department of Pathology, University of Helsinki, Helsinki, Finland

Date of submission 4 January 1999
Accepted for publication 22 April 1999
“cribriform adenocarcinoma of tongue” CAT

- In 1999 we have described eight cases of an unusual carcinoma of the tongue
- infiltrating tumor with diverse growth patterns such as solid, microcystic, cribriform and papillary
- tumor cells are bland looking with uniform, often overlapping nuclei with ground-glass chromatin
- no significant mitotic activity, necrosis or hemorrhage
Possible variant of PLGA is CAT, but it is not yet clear whether this represents a genuine entity or just an unusual growth pattern in PLGA.
Cribiform Adenocarcinoma of Minor Salivary Gland Origin Principally Affecting the Tongue: Characterization of New Entity

Alena Skalova, MD, PhD,* Radek Sima, PhD,† Jana Kaspirkova-Nemcova, Mgr,‡ Roderick H.W. Simpson, MD,‡ Goran Elmenberger, MD,§ Ilmo Leivo, MD, PhD,‖ Silvana Di Palma, MD,¶ Tomas Jirasek, MD, PhD,§ Douglas R. Gnepp, MD,** Ilan Weinreb, MD, † † Bayardo Perez-Ordoñez, MD, † † Petr Mukensnabl, MD, PhD,* Boris Rychly, MD, † † † Petr Hrabal, MD, §§ and Michal Michal, MD*

Abstract: We present a series of 23 cases of a distinctive, hitherto poorly recognized low-grade adenocarcinoma, with several histologic features reminiscent of papillary carcinoma of the thyroid, and which mostly but not exclusively occurs in the tongue. All the tumors were uncapsulated and were divided into lobules that were composed mainly of cribiform and solid growth patterns. Therefore, we propose the name “cribiform adenocarcinoma of minor salivary gland origin (CAMSG).” All the patients were adults with a mean age at diagnosis of 55.8 years (range, 25 to 85 y). Fourteen of the 23 tumors were localized in the tongue, 3 in the soft palate, 2 in the retromolar buccal mucosa, 3 in the lingual tonsils, and 1 in the upper lip. Fifteen patients of 23 had synchronous metastases in the cervical lymph nodes at the time of diagnosis, bilateral in 3 cases. In 3 patients, the nodal metastasis was the first evidence of disease, later investigation revealing primary neoplasms in the base of tongue and tonsil, respectively. In addition, 1 patient developed a cervical lymph node metastasis 8 years after excision of a primary tumor of the tongue. Data on treatment and follow-up were available in 14 cases. The patients were treated by radical excision with clear margins (12 cases) or by simple excision (2 cases). Neck dissection was performed in 10 patients; 9 received radiotherapy, but none were treated by chemotherapy. Clinical follow-up ranged from 2 months to 13 years (mean, 6 y and 5 mo). Twelve patients are alive with no evidence of recurrent or metastatic disease after treatment, 1 patient died 2 years after surgery without evidence of tumor, and 1 patient is alive with recurrent tumor of the palate.

Key Words: cribiform adenocarcinoma of minor salivary glands, tongue, polymorphous low-grade adenocarcinoma, PLGA, myoepithelial cells, hybrid secretory and myoepithelial cells


21 cases of CAT retrieved from salivary gland tumor registry:

- most cases presented in the base of tongue (13) or/and in the tonsils (2)
- followed by palate (4), lip (1), and retromolar mucosa (1)
Cribriform and tubular structure
Ground-glass nuclei („Orhan Annie eyes“) - resemble papillary ca of thyroid
Peripheral palisading and artificial clefts
Papillary growth pattern, ground-glass nuclei

TTF1, Thyreoglobulin neg

CK7, S-100, actin+
Infiltration of muscle of tongue, papillary and glomeruloid structures
Intact mucosa
neck lymph node metastasis at diagnosis in most cases of CATS
Differential diagnosis

- **PLGA polymorphous low grade adenocarcinoma**
  - Evans, Batsakis 1984
- extensive nuclear ground-glass change in CAT and much wider range of morphological diversity in PLGA
- Clinical behaviour- LN meta in most cases
Differential diagnosis

- Follicular and solid variant of papillary ca of thyroid
  - Metastatic in cervical LN
  - Primary carcinoma of thyreoglossal duct
- Thyroglobulin and TTF1 negative
- Colloid is absent
- S-100 protein and myoepithelial markers positive
CAT is a distinctive entity

- Location in tongue, tonsils, palate
- Characteristic histology different from PLGA
- Clinical behaviour
  - neck lymph node metastasis at diagnosis
  - good prognosis, no tumor related death
  - Radiotherapy is currently of unproven benefit in PLGA, CAT seem to be radiosensitive
Keratocystoma

- very rare benign tumor with only three cases having been published
- parotid gland
- children or young adults are affected
- No recurrences

Nagao et al. Mod Pathol 2002:15:1005-1010
Known entities with new findings

- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Adenomas with additional stromal components
  - Lymphadenoma
  - Lipoadenoma
  - Adenofibroma
Sclerosing mucoepidermoid carcinoma with eosinophilia

- is uncommon tumor of thyroid gland that occurs in setting of sclerosing Hashimoto thyroiditis
- it has indolent clinical behaviour
- two morphologically similar tumors of major salivary glands have been reported

Lymphadenoma

Lymphadenoma of the salivary gland: clinicopathological and immunohistochemical analysis of 33 tumors

Raja R Seethala¹, Lester DR Thompson², Douglas R Gnepp³, E Leon Barnes¹, Alena Skalova⁴, Kathleen Montone⁵, Shubhada Kane⁶, James S Lewis Jr⁷, Lynn W Solomon⁸, Roderick HW Simpson⁹, Ashraf Khan¹⁰ and Manju L Prasad¹¹

- Lymphadenomas are rare salivary gland tumors
- Their clinicopathologic characteristics and etiopathogenesis poorly understood
- Most are located in parotid gland
- Benign
- tumors are well circumscribed, encapsulated
- cut surface is gray to yellow, solid to microcystic
- epithelial nests are solid, tubular or cystic
Non-sebaceous lymphadenoma

- affect women and extraparotid sites more frequently than sebaceous tumors

CD20+
Lipoadenoma (sialolipoma)

- Benign tumor consisting of adipose tissue admixed with variable amount of adenomatous glands
- Wide age range, more males
- Oncocytic, squamous and sebaceous differentiation common

Nagao et al. Histopathology 2001:38:30-36
Adenofibroma

- Very rare benign tumor characterized by admixture of adenomatous glands and fibrocellular stroma
- Metaplastic changes and cystic dilatation common
Thank you for attention