



American Academy of Oral
& Maxillofacial Pathology

| Essay Program

Monday - June 17, 2013

8:00 am - 12:36 pm

Essay Abstracts – Monday, June 17, 2013

#1 – 8:00 am

Withdrawn

#2 – 8:12 am

AUTOANTIBODY PRODUCTION IN SJOGREN'S SYNDROME J Kramer, N Holodick, T Vizconde, T Rothstein The Feinstein Institute for Medical Research, North Shore-LIJ Health System, Manhasset Sjögren's Syndrome (SS) is an autoimmune disease that may result in significant morbidity, as patients experience xerostomia and xerophthalmia in addition to numerous systemic disease manifestations. While T cells were initially thought to be the prime drivers of SS, many recent studies detail an important role for B cells as well. At present, it is not known whether B cells derived from glandular tissue have unique characteristics as compared to those from secondary lymphoid organs. Hypothesis: B cells from salivary gland tissue have increased proliferative capacity and immunoglobulin secretion. The autoantibody profile and B cell repertoire are distinct in B cells from SS salivary tissue as compared to those from other sites. Methods: We single cell sorted B cells from spleen and submandibular tissue from SS mice, and sequenced IgM heavy chain variable regions. We then sort purified B cells derived from spleen, lymph node and submandibular tissue of SS mice. B cells were stimulated with lipopolysaccharide (LPS) and autoantigen arrays and ELISPOT and proliferation assays were performed. Results: B cells from salivary tissue of SS mice do not exhibit enhanced proliferation or elevated antibody secretion. Preliminary data suggest differences in repertoire usage may be present in B cells derived from salivary tissue compared to those from spleen. Moreover, autoantigen array data suggest B cells derived from salivary tissue display distinct autoantibody specificities as compared to those from spleen and cervical lymph nodes. Conclusion: All together, these data suggest antibodies from salivary gland B cells have unique characteristics that likely influence autoantigen binding and contribute to SS disease in a tissue specific manner.

Essay Abstracts – Monday, June 17, 2013

#3 – 8:24 am

EVALUATION OF ANGIOGENESIS IN ORAL LICHEN PLANUS: AN IMMUNOHISTOCHEMICAL STUDY WITH CD34 AND ENDOGLIN M Khalili, N Eshghyar, M Asgari Tehran U of Medical Sciences, Tehran Background and aim: Angiogenesis is a major component of neoplastic and chronic inflammatory disorders but its role in mucocutaneous inflammatory diseases such as oral lichen planus (OLP) has not been established yet. The aim of this study was to determine the angiogenic potential of OLP compared to normal oral mucosa. Materials and methods: 15 cases of reticular and 15 cases of erosive oral lichen planus were selected. Fifteen samples of normal oral mucosa were used as control group. 4-micrometer sections were cut from paraffin blocks and stained with CD34 and CD105 antibodies. Microvessel counting was performed in areas of highest vascularity (hot spots). Data were analyzed by ANOVA and post hoc tests. $P < 0.05$ was considered as the limit of significance. Results: CD34 staining showed a mean microvessel density (MVD) of 6.05 ± 0.86 in normal mucosa compared to 16.65 ± 3.34 and 31.8 ± 5.39 in reticular and erosive lichen planus, respectively. CD105 staining showed a mean microvessel density (MVD) of 1.7 ± 0.77 in normal mucosa, 9.13 ± 1.81 and 19.05 ± 3.02 in reticular and erosive lichen planus respectively. Intergroup analysis showed significant differences in MVD among the studied groups for both markers ($P < 0.001$). Conclusion: Based on our findings, microvessel density was higher in OLP compared to normal oral mucosa which could be related to a potential angiogenic influence in the pathogenesis and progression of the disease.

#4 – 8:36 am

MATRIX METALLOPROTEINASE IN ORAL VESICULOEROSIVE DISEASE-ANALYSIS AND THERAPEUTIC MODULATION WITH SUBANTIMICROBIAL DOSE DOXYCYCLINE: A PILOT STUDY T Jhamb, JM Kramer, JE Fantasia Hofstra North Shore-LIJ School of Medicine, New Hyde Park; State University of New York, Buffalo Matrix metalloproteinases (MMP) 2 and 9 have been studied in human inflammatory diseases. Oral vesiculoerosive diseases (VED) include chronic pathoses such as cicatricial pemphigoid (CP) and lichen planus (OLP). Treatment with subantimicrobial dose doxycycline (SDD) inhibits MMPs and is used in treatment of other chronic inflammatory processes. MMP 2 and 9 ELISAs were performed on sera, saliva and urine of healthy controls to establish baseline levels. HYPOTHESIS: MMP 2 and 9 is increased in sera, saliva, and urine of patients with OLP and CP as compared to healthy subjects. SDD treatment mitigates inflammatory reaction in OLP and CP resulting in clinical improvement through diminishing MMP expression. METHODS: Sera, saliva and urine from VED patients were sampled at baseline, and at two time points following initiation of SDD therapy. Sera, saliva, and urine were also collected from healthy controls. ELISAs were used to compare the levels of MMP 2 and 9 in these fluids from healthy controls ($n=10$) and VED patients, prior to SDD therapy ($n=7$). In addition we used ELISAs to monitor MMP 2 and 9 levels during therapy in VED patients ($n=5$). RESULTS: Preliminary data indicate increased MMP 2 in sera ($p=0.0046$) and saliva ($p=0.0121$) in VED patients as compared to healthy controls. MMP 9 levels in saliva were elevated, but did not achieve statistical significance. In addition, preliminary data show decreased MMP 2 and 9 levels in patients receiving SDD. CONCLUSION: MMP 2 levels are increased systemically in VED patients compared to healthy controls. SDD may reduce expression of MMP 2 and 9 in VED. SDD may be an important therapeutic approach to reduce the chronic inflammation characteristic of VED by modulation of MMP expression. Additional study subject accrual is ongoing.

Essay Abstracts – Monday, June 17, 2013

#5 – 8:48 am

HISTOLOGIC LICHENOID FEATURES IN ORAL DYSPLASIA AND SQUAMOUS CELL CARCINOMA S Fitzpatrick, K Honda, A Sattar, S Hirsch Case Western Reserve University, Cleveland Histologic features associated with the immune-mediated chronic inflammatory condition oral lichen planus (OLP) have been observed in some premalignant oral lesions, a phenomenon that could increase the risk of erroneous or delayed diagnosis. This study retrospectively examined 352 histologic specimens of oral low grade (LG) dysplasia, high grade (HG) dysplasia, and squamous cell carcinoma (SCCA) for five histologic characteristics commonly associated with OLP: band-like inflammatory cell infiltrate sub-adjacent to the epithelium (BLI), saw-tooth rete ridge formation (SRR), interface stomatitis (IS), Civatte bodies (CB), and degeneration of the basal layer (DBL). These lichenoid characteristics were evaluated in regards to grade of dysplasia/SCCA, age, gender, and oral cavity sub-site. Twenty-nine percent of the cases exhibited three or more features and met a threshold for overall lichenoid characteristics. BLI was the most common and nonspecific feature noted in almost three-quarters of cases, followed in descending order by IS, DBL, CB, and SRR. Lichenoid features were significantly more frequent in LG lesions than HG lesions. No statistically significant pattern was noted for age or gender. The oral cavity sub-site also showed statistically significant differences in lichenoid characteristic frequency with the buccal mucosa overrepresented and the floor of the mouth underrepresented in relation to the frequency of involvement in SCCA. The study is significant for demonstration of frequent correlation of lichenoid features with certain oral premalignant and malignant lesions. This study also highlights the subjective nature of the assessment of lichenoid features in premalignant and malignant oral lesions which further complicates accurate and consistent diagnosis.

#6 – 9:00 am

HPV-ASSOCIATED ORAL EPITHELIAL DYSPLASIA: A DISTINCT HISTOPATHOLOGIC ENTITY S Almazrooa, M Lerman, V Noonan, S-B Woo Harvard School of Dental Medicine, Boston; Strata Pathology Services, Lexington, Brigham and Women's Hospital, Boston Background: The incidence of oropharyngeal and particularly tonsillar squamous cell carcinoma (SCC), has increased, possibly as a result of high-risk human papillomavirus (HPV) infection. Recognition of HPV-SCC in the oropharynx is important because of its more favorable prognosis. In the oral cavity, the association of SCC with HPV is low and the precursor dysplastic lesion has yet to be well-characterized. Objectives: The aim of this study is to describe the histopathologic features of HPV-associated oral epithelial dysplasia (OED) and compare them to non-HPV-associated OED. Findings: Eight cases were identified in six men and two women (median age: 65.5 yrs). Five cases involved the ventrolateral tongue. Bright parakeratin was present in seven cases and severe dysplasia was present in all cases. The mean numbers of karyorrhectic and apoptotic cells were 5.9 and 5.3 respectively at 600X magnification. All cases expressed p16 in a continuous band that coincided with the presence of high-risk HPV subtypes by in situ hybridization while probe for low-risk subtypes was negative. All controls exhibited moderate to severe OED; the mean numbers of karyorrhectic and apoptotic cells were 0.6 and 1, respectively. All controls were negative for p16 stain. Conclusion: HPV-associated OED primarily affects men over the age of 60 and often involves the ventrolateral tongue. It is characterized by marked apoptosis and karyorrhexis, severe epithelial dysplasia, p16 reactivity, and positivity for high risk HPV subtypes. Recognition and follow-up for malignant transformation may help better characterize the role of HPV in oral SCC development.

Essay Abstracts – Monday, June 17, 2013

#7 – 9:12 am

INVASIVE FRONT HISTOLOGY OF ORAL SQUAMOUS CELL CARCINOMA CORRELATES WITH OVERALL STAGE AND OVERALL SURVIVAL K Byrd, J Fox, E Bellile, G Wolf, T Danciu U of Michigan, Ann Arbor **AIM:** To study invasive fronts of OSCC biopsies, comparing histological assessments of E-cadherin expression and localization (indicators of EMT) as well as Bryne's classification with techniques used in prostate (Gleason) and colorectal cancer (tumor budding). **METHODS:** 53 biopsies with clinical characteristics were retrieved. Pan-cytokeratin immunohistochemistry (IHC) was performed to assess tumor budding and pattern of invasion. Bryne's classification was determined traditionally ('overall') and at the site with the most pronounced EMT ('worst'). Gleason score was analyzed as a combination of Bryne's 'overall' (>50%) and Bryne's 'worst' site (>10%). Tumor budding score and count were obtained at the invasive front. E-cadherin expression and localization were evaluated on the basis of IHC staining, both at 'overall' and 'worst' sites of the invasive front. Chi-square testing was performed with Monte Carlo estimate. **RESULTS:** Median follow-up for overall patient survival was 25 months; 17 patients had died as of the preliminary analysis. There is statistical significance between Bryne's 'overall' classification and tumor budding count with overall stage ($p=0.02$). Currently, there is no statistical correlation with Gleason score. Overall loss of membranous E-cadherin is statistically associated with higher stage ($p=0.005$) as well as with a higher tumor budding count ($p=0.004$). Loss of E-cadherin at the 'worst' site has borderline significance with survival (0.049). No association was observed between histological assessment of the other factors and overall survival, which may be due to relatively short follow-up period. **CONCLUSION:** Our preliminary study represents a first step in the development of a mathematical risk model for OSCC patients.

#8 – 9:24 am

PI3K/MTOR INHIBITOR PF-04691502 SUPPRESSES TUMOR GROWTH, IMPROVES SURVIVAL, AND REACTIVATES TP53 IN HUMAN XENOGRAFT AND MURINE TRANSGENIC HEAD AND NECK CANCER MODELS R Vander Broek, Y Bian, A Herzog, B Hall, J Coupar, Z Chen, A Kulkarni, C. Van Waes National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, Bethesda The oncogenic PI3K-Akt-mTOR and tumor suppressive TP53 axes are two of the most frequently dysregulated and pathogenic signaling cascades in head and neck squamous cell carcinoma (HNSCC). They include important therapeutic targets which could serve as useful biomarkers to monitor HNSCC progression and/or therapeutic activity. In this study, we investigated the in vitro and in vivo effects of a molecular antagonist of PI3K and mTOR, PF-04691502 (PF-502), on PI3K/mTOR targets, TP53 activity, and HNSCC tumorigenesis. A panel of HNSCC cell lines was surveyed which exhibited elevated expression of PI3K/mTOR pathway proteins, including PI3K, pAKT, pmTOR, p4EBP1, and S6. PF-502 inhibited phosphorylation of these PI3K/mTOR targets and reactivated TP53 and its family member, p73. PI3K/mTOR target inhibition and TP53/p73 induction in vitro correlated with decreased cellular proliferation and increased apoptosis. TP53 inhibition by pifithrin- \pm attenuated the effects of PF-502 on cell growth inhibition. These in vitro drug effects remained consistent in two separate in vivo models: 1) human HNSCC xenografts in SCID mice, and 2) Pten/Tgfr1 double knockout mice, which develop HNSCC spontaneously. PF-502 inhibited or prevented tumor growth and prolonged host survival in both in vivo models. After drug treatment, decreased pAKT, p4EBP1, pS6, Ki67, as well as increased TP53, p73, and TUNEL were observed in tumor specimens. Thus, PF-502 improves survival and inhibits the development and progression of HNSCC in preclinical models. Decreased pAkt, p4EBP1, pS6, and increased TP53/p73 expression correlate well with the antitumor effects of PF-502 in HNSCC, warranting further investigation of PI3K/mTOR inhibitors in a clinical subset of patients with overactive PI3K/mTOR and defective TP53.

Essay Abstracts – Monday, June 17, 2013

#9 – 9:36 am

NEUROPILIN-1 AND ORAL SQUAMOUS CELL CARCINOMA SS Farahani, K Munger, K Hida, M Gallottini, D Bielenberg Harvard School of Dental Medicine and Department of Medicine, Harvard Medical School, Boston; Division of Oral Pathobiological Science and Vascular Biology, Hokkaido University Graduate School of Dental Medicine, Sapporo, Japan; Department of Oral Pathology, School of Dentistry, University of São Paulo, São Paulo, Brazil; Department of Surgery, Harvard Medical School and Vascular Biology Program, Karp Family Research Laboratories, Boston Children's Hospital

Angiogenesis is one of the most important prognostic factors in oral squamous cell carcinoma (SCC). Neuropilins (NRPs) are transmembrane receptors that bind VEGF and class 3 semaphorins (SEMA3). Upregulation of neuropilin-1 (NRP1) and its effect on angiogenesis, lymphangiogenesis, and the metastatic process has been shown in some human carcinomas. Western blotting, ELISA, and IHC were performed on selected human tongue SCC (HTSCC) cell lines and specimens of HTSCC and dysplasia to evaluate NRP1 or VEGF expression. Selected HTSCC cell lines were injected into nude mice subcutaneously or in the tongue. Resected tumors were evaluated for NRP1 expression, angiogenesis, and lymphangiogenesis by IHC. Normal isolated and calcium treated primary mouse keratinocytes were compared for Nrp1 expression. Proliferation, collapse, and migration assays were performed on HTSCC cell lines after adding SEMA3A. HTSCC cell lines and tissue sections showed differential NRP1 expression. Normal mouse tongue expressed Nrp1 in the suprabasal epithelium, while dysplastic lesions strongly demonstrated NRP1 expression in the basal cell layer. Resected tumors showed NRP1 expression. Primary mouse keratinocytes treated with calcium showed more differentiation which was correlated with Nrp1 expression. SEMA3A treatment did not affect proliferation, but induced collapse and inhibited migration of HTSCC cell lines. Conclusions: Some HTSCC cell lines and tumors express NRP1 which is correlated with VEGF production, degree of invasiveness of these cell lines, and angiogenesis. Epithelial dysplastic lesions express NRP1 which may correlate with the degree of dysplasia. Calcium may regulate Nrp1 expression. SEMA3A treatment may be a potential therapy to inhibit the spread of oral SCC.

#10 – 9:48 am

GALANIN RECEPTOR 2 PROMOTES TUMOR ANGIOGENESIS IN HEAD AND NECK CANCER R Banerjee, EA Van Tubergen, C Scanlon, R Vander Broek, M Liu, JP Lints, N Russo, RC Inglehart, Y Wang, P Polverini, K Kirkwood, NJ D'Silva U of Michigan, Ann Arbor

Squamous cell carcinoma of the head and neck (SCCHN) is an aggressive disease with poor patient survival. Galanin receptor 2 (GALR2) is a G-protein coupled receptor (GPCR) that induces aggressive tumor growth. Since GPCRs have multiple effects on tumor progression, we investigated whether GALR2 promotes angiogenesis in SCCHN. To address this impact, we used biochemical and molecular approaches in human SCCHN cells in in vitro and in vivo models of human SCCHN. In vivo models included the murine floor-of-mouth syngeneic, orthotopic model of SCCHN and a recently developed model of SCCHN-related angiogenesis using the chick chorioallantoic membrane. GALR2 stimulated angiogenesis by activation of p38 MAPK and by enhanced secretion of pro-angiogenic cytokines, VEGF and IL-6. This occurred via rap1B-p38 MAPK-mediated phosphorylation of tristetraprolin (TTP), an RNA-binding protein that facilitates degradation of cytokine transcripts. Moreover phosphorylation-mediated inactivation of TTP in SCCHN cells overexpressing GALR2 further increased secretion of IL-6 and VEGF. Given its significant role in promoting tumor progression, GALR2-p38 mediated cytokine secretion may be an excellent target for adjuvant therapy in SCCHN. This study was financially supported by NIH/NIDCR grants DE018512 and DE019513 (NJD), DE021293 (CSS), DE021305 (EVT).

Essay Abstracts – Monday, June 17, 2013

#11 – 10:00 am

EXPRESSION OF P8 IN HUMAN ORAL SQUAMOUS CELL CARCINOMA K Ogbureke, C Bingham, D Dickinson U of Texas School of Dentistry, Houston; Georgia Regent U, Augusta
Objective: Study investigates the expression and potential role of p8, a transcription factor that exhibit paradoxical roles in several human cancers, including human oral squamous cell carcinomas (OSCC). The mortality rate from oral cancer for the past four decades remains over 50%. Because early detection and treatment increase the survival rates of patients, the search for reliable predictors of OSCC progression and prognosis remains relevant. Methods/Principal Findings: Analysis of the immunohistochemical expression of p8 was carried out on 20 archived surgical specimens of human OSCCs, and expression correlated with clinical/outcome parameters in a retrospective study. Also, levels of p8 in OSCC cell line, OSC2, before and after lentiviral-mediated shRNA p8-silencing as well as the effects of silencing on notable hallmarks of oral carcinogenesis were assayed by western blot, RT-PCR, and MTT (cell-viability) assay. p8 was expressed in 85% (17/20) of OSCCs with levels of expression (means and SD+/-) exhibiting a significant difference ($\chi^2=8.352$, $df=3$, $p=0.039$) for age. Furthermore, the predictive regression models for p8 immunoreactivity versus the degree of histologic differentiation of tumor on H sections (HE-DIFF) was significant ($p=0.008$). p8-silenced OSC2 cells exhibited altered cell morphology, ~53% decrease in cell proliferation ($p,0.05$; $n=3$), and a significant downregulation of Ki-67 (~50%), CEBP (~50%), and Nrf1(~50%). Conclusion: p8 is expressed in a significant number of OSCCs. p8-silencing decreases the viability/proliferative potential of OSC2 cells, suggesting a role for p8 in pathways involving proliferation markers critical for oral cancer progression. The data provides a framework for future studies on p8 mechanistic networks in oral cancer biology.

#12 – 10:12 am

APPLICATION OF A BLACK RASPBERRY GEL (BRB) INDUCES HISTOLOGIC & CLINICAL REGRESSION OF ORAL INTRAEPITHELIAL NEOPLASIA (OIN) SR Mallery, M Tong, B Shumway, A Curran, P Larsen, G Kushner, G Blakey, G Ness Ohio State U, Columbus; U of Louisville, Louisville; U of North Carolina, Chapel Hill
Therapeutic efficacies of BRB and placebo gels on OIN (0.5 gm q.i.d. x 3 months) were determined by effects on: 1) histologic grade, 2) clinical size, 3) LOH indices at putative tumor suppressor gene loci associated with OIN progression to OSCC, 4) lesional epithelial levels of COX-2, iNOS, microvascular densities (MVD), 5) methylation of p16 promoter regions. Pretreatment OIN biopsies provided a microscopic diagnosis and baseline biomarkers. Metabolic profiling analyses were also conducted. Placement in the BRB ($n=22$) and placebo ($n=18$) gel groups was randomized. Pretreatment parameters (grade, size, LOH indices) were comparable between the BRB and placebo cohorts. Trial results have shown: 1) No deleterious effects, 2) BRB gel decreased OIN clinical size (BRB $p=0.0019$) whereas 17/18 placebo gel lesions increased ($p=0.0395$) 2-tailed Mann Whitney U test., 3) BRB gel reduced OIN histologic grade (BRB $p=0.0488$, placebo $p=0.4961$, Wilcoxon matched-pairs signed-rank test), 4) BRB gel reduced LOH indices at 9p markers (BRB $p=0.0156$, placebo $p=0.9999$, Wilcoxon matched-pairs signed-rank test), 5) Comparable 3 month recurrences. Analyses of COX-2, iNOS and MVD, metabolic profiles (Westerns), LOH analyses at p53 and FHIT loci, and p16 promoter methylation studies are ongoing. Our results confirm that BRB constituents-and not gel base components-provide the chemopreventive activity and demonstrate clinically relevant efficacy. As many key BRB active constituents are redox active molecules, we speculate that dysplastic phenotype reduction reflects redox-mediated modulation of gene expression and induction of apoptosis. The comparable recurrence rates imply persistence of altered stem cells and suggest a need for sustained treatment.

Essay Abstracts – Monday, June 17, 2013

#13 – 10:24 am

ORAL CANCER DETECTION: A COMPARATIVE STUDY IN ARGENTINA H Lanfranchi, M Labrozzi, M Velazco, M Gandolfo Department Of Oral Medicine, School Of Dentistry, U Of Buenos Aires Although oral cancer is accessible to inspection and diagnosis, due to its location, referral to specialists occurs in advanced stages. Late diagnosis in oral cancer is a universal problem that causes high morbidity and low patient survival. We study clinical features, histopathological diagnosis, localization, clinical stage and survival of oral squamous cell carcinoma (OSCC) in two periods: 1992-2000 and 2001-2009. This work comprised 507 patients diagnosed with OSCC who attended our Oral Medicine Department. Tumor location, clinical and histopathological diagnosis, clinical staging and patient follow-up were recorded on a digital database. Statistical analysis was performed using the comparison test of proportions and prognostic assessment of survival was performed employing Kaplan Meier's test. Tumor staging corresponding to the 1990-2000 period was 23.6% in early stages and 76.3% in late stages whereas in the 2001-2009 period showed 49.3 % in early stages and 50.7 % in late stages ($p < 0.001$). Tongue localization corresponding to the 1992-2000 period was 26.49% in early stages and 73.48% in late stages and in the 2001-2009 period was 64.4% in early stages and 35.61% in late stages ($p < 0.05$). The survival rate of OSCC in the first decade was 38% and the second was 64% ($p < 0.0004$) after 60 months. Results showed a significant increase in the survival rate in the period 2001-2009. This raise was related to increased survival in the location of the tongue in this last decade. This favorable prognosis would be mainly due to the amount of cancer cases that were diagnosed in early stages because of the implementation of new teaching methods, as well as the oral cancer prevention programs developed in the last decade in Argentina.

#14 – 10:36 am

THE CLINICAL APPEARANCE OF ORAL MUCOSAL MALIGNANCIES: RE-EVALUATION OF COMMON PARADIGMS I Allon, DM Allon, G Gal, Y. Anavi, G Chaushu, I Kaplan Rabin Medical Center, Petach-Tikva and Tel-Aviv U, Tel Aviv Purpose: To evaluate the clinical appearance and rate of ulceration of oral mucosal malignancies, and investigate the accuracy of clinical provisional diagnoses. Methods: 10 year retrospective analysis. Results: 227 oral mucosal malignant tumors were included. SCC and its variants accounted for the majority (78%) of malignant tumors. The most common clinical presentations were non-ulcerated (59.7%) and ulcerated masses (20.4%). Only 11.9% presented as indurated ulcers. The highest ulceration rate of all malignancies was recorded for SCC, with only about half of SCC and its variants ulcerated at presentation. Approximately a third of cases were not suspected for malignancy clinically, reflecting a false negative rate of 31.1%, with lower false negative rates in ulcerated tumors. There was better agreement between clinical and microscopic diagnoses in the SCC group than in other types of malignancy ($p < 0.001$). Conclusion: The majority of oral mucosal cancers were non-ulcerated. Non-ulcerated mass was by far a more common clinical appearance than were indurated ulcers. Although the study was performed in a training center for OMF surgery, the false negative rate for clinical diagnosis of malignancy approached a third of all malignancies, with the highest rates in tumors lacking surface ulceration. To improve the reliability of clinical diagnosis of malignancy in oral mucosa, non-ulcerated masses should be regarded with a higher level of suspicion, parallel to suspicion levels currently reserved for mucosal ulcers and ulcerated masses.

Essay Abstracts – Monday, June 17, 2013

#15 – 10:48 am

MACRO- AND MICROSCOPIC OPTICAL IMAGING TOWARD DIAGNOSIS OF ORAL EPITHELIAL DYSPLASIA B Malik, J Jabbour, S Cheng, R Cuenca, J Jo, J Wright, Y Cheng, K Maitland Texas A&M U, College Station; Texas A&M Health Science Center, Baylor College of Dentistry, Dallas

Clinical guidelines for early detection of oral cancer include screening examination wherein the clinician visually inspects and palpates the high-risk sites for development of oral cancer. The actual evaluation of risk then usually requires one or more biopsies, the location(s) of which are increasingly critical to identify. Therefore, development of noninvasive clinical tools that can help the clinician identify the most accurate sites of precancerous lesions is of great importance and can potentially increase the diagnostic yield of the overall screening process. To this end, we have developed a multi-modal, multi-scale imaging system based on macroscopic fluorescence lifetime imaging (FLIM) and high resolution reflectance confocal microscopy (RCM). In the current study, we used the Syrian hamster cheek pouch DMBA model of carcinogenesis. FLIM provided the biochemical screening by probing the endogenous fluorescence of structural proteins (collagen) and metabolic cofactors (NADH, FAD), and RCM provided information on nuclear morphology and overall tissue architecture. The results show that qualitative differences between normal, precancerous and cancerous sites were resolved with FLIM/RCM imaging, and correlated well with the histopathological evaluation. While FLIM allowed for distinguishing between normal and cancerous tissue, RCM was still necessary for identifying cellular changes associated with dysplasia. Such a simultaneous assessment of tissue physiology/morphology can help identify the diagnostic state of the oral tissue. This study suggests that FLIM/RCM imaging can serve as a guiding tool for standard screening methods, and provides the ground work for application of this multi-scale imaging modality in a clinical setting.

#16 – 11:00 am

INTRAORAL BASAL CELL CARCINOMA: REPORT OF TWO NEW CASES WITH LITERATURE REVIEW T Woods, D Cohen, NM Islam, I Bhattacharyya University of Florida, Gainesville

Intraoral basal cell carcinoma (IOBCC) is an extremely rare entity that is often confused with the peripheral ameloblastoma (PA). Basal cell carcinomas are thought to arise from pluripotential basal cells present within surface epithelium and adnexal structures, so theoretically they can arise within the oral cavity. Most of the well documented cases arise from the gingiva. Many of the early cases reported as IOBCC actually represent PA. We present 2 cases displaying histologic, immunohistochemical and clinical features characteristic of an IOBCC. The histologic features of IOBCC that help separate it from a PA include: prominent retraction artifact, tumor arising from surface epithelium, scattered mitotic figures and apoptotic cells, presence of mucoid ground substance and tumor infiltrating widely throughout the connective tissue. Clinically IOBCC resemble carcinomas compared to the benign appearance and innocuous appearance of the PA. IOBCC typically present as surface ulcerations varying from rodent ulcer to an ulcerated erythroplakic appearance. This contrasts with the classic “bump on the gum” appearance of PAs with usually intact surface and appearing as small discrete, sessile, exophytic lesions. In the more recent literature, Del Rosario et al and Koutlas et al described IOBCC with positive immunoreactivity of only the neoplastic basal cells for the anti-epithelial antibody, Ber-EP4, a cell surface glycoprotein. Normal skin or oral epithelium, PA and squamous cell carcinomas do not stain with Ber-EP4, a very important distinguishing factor separating these entities.

Essay Abstracts – Monday, June 17, 2013

#17 – 11:12 am

HISTOLOGIC AND IMMUNOHISTOCHEMICAL DIFFERENTIATION BETWEEN GLANDULAR ODONTOGENIC CYSTS AND CYSTS WITH FEATURES OF GLANDULAR ODONTOGENIC CYST
L Montague, A Neuman, K Kimbler, NM Islam, D Cohen, I Bhattacharyya U of Florida Gainesville
Glandular odontogenic cysts (GOC) are relatively uncommon, distinct developmental odontogenic cysts with unusual histopathologic features. Due to the overlap of key microscopic features with other developmental cysts, particularly dentigerous cysts, it is imperative that stringent criteria and specific markers be identified. Immunohistochemistry has been studied to aid differentiation of GOC from other cysts. Tosios et al, with a very limited sample size, reported increased expression of bcl-2 in GOCs compared to dentigerous cysts. Aim: To determine whether GOCs can be consistently differentiated from other cysts based on histologic features and to compare bcl-2 expression in GOCs and other cysts with features of GOC. Methods & Materials: We identified 141 cases from 1994 to 2012 coded as GOC or cysts with some features of GOC. Four study participants categorized these as “GOC” or “non-GOC cyst” using criteria established by Fowler et al. Of these, 15 cases were initially selected and stained for bcl-2. Results: A total of 23 cases were categorized by all reviewers as GOC. Fifteen cases were agreed to be “non-GOC”. The remaining cases were designated as “equivocal” with significant inter-observer disagreement. All stained cases diagnosed as GOC were strongly bcl-2 positive in the basal and suprabasal cell layers. The non-GOC cysts were minimally to focally positive for bcl-2. Conclusions: True GOCs can be difficult to distinguish histologically from cysts with some features of GOC. Bcl-2 staining appears to be consistently strong in GOC and therefore, may be a useful discriminator when limited clinical information is available and overlapping microscopic features are present.

#18 – 11:24 am

INTERPRETATION OF SOX2 IMMUNOHISTOCHEMICAL STAIN IN AMELOBLASTIC CARCINOMA: AN EXPANDED COHORT
Y Lei, J Jaradat, A Owosho, K Adebisi, B Neville, S Müller, E Bilodeau U. of Pittsburgh, Pittsburgh; Emory U, Atlanta; Obafemi Awolowo U, Ife; Medical U of South Carolina, Charleston
SOX2 (sex determining region Y-box 2), originally identified as a pivotal transcription factor for epithelial renewal, is found to be overexpressed in a spectrum of epithelial malignancies. As an odontogenic epithelium-derived cancer, ameloblastic carcinoma (AC) often poses diagnostic challenges especially in its separation from benign ameloblastoma with atypical cytological features or unusual clinical course. In our previous publication, we identified SOX2 as a marker for high grade transformation in ameloblastic neoplasms with only 2 stained AC cases. Here we include an additional 8 AC cases to provide a more comprehensive interpretation. SOX2 marks the basal proliferative zone of epithelium in dentigerous cysts. It is negative in mature epithelium and ameloblastic neoplasms without high grade transformation. The diffuse strong nuclear staining pattern has 100% specificity to indicate the presence of high-grade features (7/7), and 70% sensitivity (7/10) in comparison with other benign ameloblastic neoplasms (P=0.039). Although previously shown as a promising marker for ameloblastic neoplasms, calretinin is weakly positive in a few cells in 50% (5/10) of AC and 43% (3/7) benign ameloblastic neoplasms with little value in highlighting the high grade change (P=0.36). Diffuse nuclear stain pattern of SOX2 is suggestive of a high grade process in ameloblastic neoplasms. Focal aggregates of cells harboring dense nuclear stain should raise caution for a malignancy arising in ameloblastoma with otherwise classical benign features. This is conceptually consistent with recent studies that show increased SOX2 expression is associated with a poorer prognosis in oral cancer, sinonasal cancer, and urothelial cancer.

Essay Abstracts – Monday, June 17, 2013

#19 – 11:36 am

MAMMARY ANALOG SECRETORY CARCINOMA: 20 CASES IN MINOR SALIVARY GLANDS J Wollenberg, S Wetzel, J Kacher, P Freedman New York Hospital Queens, Flushing; JKJ Pathology, Spring

Mammary analog secretory carcinoma (MASC) is a newly recognized salivary gland tumor with a unique histologic appearance, immunohistochemical profile, and chromosomal translocation. In the seminal paper, these tumors are described as circumscribed, lobulated masses with microcystic, tubular and solid structures. To date, 89 cases of MASC have been reported. Of those cases, only 21 were located intraorally. We present an additional 20 cases of MASC involving the minor salivary glands. Microscopically, these tumors are locally infiltrative and composed of mildly pleomorphic cells with abundant eosinophilic and granular cytoplasm. The majority of the minor salivary gland tumors are arranged in solid, microcystic and tubular growth patterns. However, 8 of the 20 cases in this series consisted of one or more cysts lined by tumor cells with papillary projections extending into the cyst lumen. These tumors are described as having a papillary cystic morphology. Immunohistochemistry shows these tumors to be positive for S100, mammaglobin and vimentin with variable positivity for GCDFP-15. This is similar to the staining pattern of secretory carcinoma of the breast, which is consistently positive for S100 and mammaglobin. Although fluorescence in situ hybridization reveals consistent t(12;15) this may not be practical for routine diagnosis in most laboratories. A recent publication suggests the use of histopathologic features along with strong immunohistochemical positivity for S100 and mammaglobin as diagnostic criteria. These additional cases help to further refine the histologic spectrum of mammary analog secretory carcinoma.

#20 – 11:48 am

ISOLATION OF CEMENTUM PROTEIN (CEMP-1) IN A CEMENTOBLASTOMA B Aldape Barrios, LH Rodriguez, H Arzate, ME Monroy, RS Lopez, DR Diaz Miron, BC Legorreta UNAM and Centro Medico Siglo XXI, Mexico City

In recent years cementum protein (CEMP-1) has been isolated from human cementoblastoma CEMP-1 its considered as a specific marker of cementoblasts, periodontal progenitor cells and mineralization process such as octacalcium phosphate crystal nucleation of hydroxyapatite precursor. Also, CEMP -1 has been observed to induce phenotypes differentiation of periodontal ligament cells toward the cementoblastic/ osteoblastic and chondroblastic. The aim of this study is to identify the presence of cementum protein (CEMP1) in a lower right first molar cementoblastoma. Twenty six years old male right mandibular. An orthopantomography image showed a well-defined radiopaque lesion in the lower right first molar region. The excisional biopsy showed cementum-like tissue, prominent basophilic reversal lines, and fibrous connective tissue as a capsule. An immunofluorescence study was performed with the use of polyclonal antibody against CEMP1 at a 1:100 concentration diluted with BSA. Subsequently, a secondary goat anti-rabbit antibody labeled with fluorescein isothiocyanate (FITC, Santa Cruz Biotechnology, Inc.) in a 1:75 concentration was incubated according to manufacturer's instructions and with PBS 1x diluted for two hours at room temperature. At the end, two more washes with PBS 1x were performed. As a negative control the same procedure was done but with the absence of the primary antibody. The expression of CEMP 1 were positive in subpopulations cementoblasts and mineralized tissue. The CEMP-1 could help to identify and standardization of the tumoral lesions like cementoblastoma.

Essay Abstracts – Monday, June 17, 2013

#21 – 12:00 pm

PAPILLARY CYSTADENOCARCINOMA ARISING IN PAPILLARY CYSTADENOMA OF THE SUBLINGUAL GLAND A Cohen, I Kaplan, G Grenkel, B Shlomi, V Raiser Tel-Aviv Sourasky Medical Center and Tel-Aviv U, Tel Aviv Papillary cystadenoma (PCA) and its malignant counterpart papillary cystadenocarcinoma (PCAC) are both rare neoplasms in sublingual salivary glands. There is considerable overlap in microscopic characteristics with PCA being encapsulated while PCAC infiltrative. Atypia, necrosis or increased mitotic activity may not be present. We report a sublingual tumor in a 78 years old woman, present for several years and stable in size, presenting gradual growth for 4 months. A multi-lobulated, non-ulcerated, bluish submucosal mass of 4 cm diameter occupied the floor of mouth. MRI identified a well circumscribed, multicystic mass, located above the mylohyoid and replacing the sublingual gland. Biopsy exhibited multi-luminal cystic architecture. The lining epithelium was thin, composed of uniform cuboidal cells, creating delicate luminal papillary projections. The cytology was bland, lacking atypia, prominent mitotic activity or necrosis, and the diagnosis was PCA. During surgery the lesion seemed to present a distinct capsule and separated easily by extra-capsular dissection. However, in the most posterior region, firm attachment to the submandibular gland area was observed. The microscopic analysis of the resection specimen showed features identical to the biopsy, with a clear capsule in the majority of the periphery, except for the posterior aspect, where a clear infiltrative pattern was observed. The final diagnosis was reversed to PCAC. The history of a long duration with a recent increase in size, the encapsulation of most of the tumor periphery and the localized front of invasion all suggest transformation from PCA to PCAC. This has never been described before in this particular tumor type, although it is well-recognized in long-standing pleomorphic adenoma.

#22 – 12:12 pm

DENDRITIC CELL NEUROFIBROMA WITH PSEUDOROSSETTES: A REPORT OF FIVE INTRAORAL CASES C-C Li, MA Lerman, V Noonan, S-B Woo Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston; Department of Oral Pathology, Boston U School of Dental Medicine, Boston Dendritic cell neurofibroma with pseudorosettes (DCNP) is a rare benign peripheral nerve sheath tumor first described in 2001 by Michal et al. Only 25 cases (26 lesions) have been published in the English literature with no intra-oral lesions reported to date. DCNP has been reported in adults with no gender predilection; the mean age was 46.5 years (range 24-73). DCNPs commonly present as well-circumscribed, dome-shaped, firm nodules in the dermis of the trunk (40%), extremities (32%), or the head and neck region (28%). DCNP is characterized by a biphasic population of neural cells with S-100 and CD57 positivity. Type I cells are small and lymphocyte-like with dark nuclei; type II cells are large neural ganglion-like with pale, vesicular nuclei showing intranuclear pseudoinclusions. Type I cells are generally arranged concentrically around centrally-located Type II cells, forming pseudorosettes. The tumor cells are negative for neuroendocrine, muscular, and epithelial markers. There is no reported tendency for lesional recurrence or malignant transformation after complete excision. We present a series of five cases of DCNP, the first report of intra-oral lesions. The lesions presented in two males and three females, with a mean age of 53.4 years (range, 36-73). Three presented on the buccal mucosa and two on the tongue. Each tumor demonstrated all the characteristic features of DCNP. Both cell populations exhibited strong S-100 positivity. Strong CD57 positivity was consistently demonstrated in type II cells and was variable among type I cells. Pathologists should consider DCNP in their differential diagnoses when confronted with unusual neural lesions that do not exhibit classic features of neurofibromas, schwannomas, or other benign peripheral nerve sheath tumors.

Essay Abstracts – Monday, June 17, 2013

#23 – 12:24 pm

TWO CASES OF EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR WITH INITIAL PRESENTATION IN THE MANDIBLE A Boros, S Kashikar, R Wiley, J Baker, H Dym, R Reich, P Freedman New York Hospital, Queens; Private Practice, Mount Kisco; Brooklyn Hospital, Brooklyn

Ewing sarcoma and primitive neuroectodermal tumor (ES/PNET) represent opposite ends of a spectrum of malignant round cell neoplasms that show variable degrees of neuroectodermal differentiation. Initial presentation of ES/PNET in the oral cavity is exceedingly rare and involvement of the gnathic or craniofacial region occurs in approximately 1-2% of cases. We contribute two cases of ES/PNET presenting as enlarging mandibular radiolucencies from a 5 year old male and a 34 year old male. Although ES/PNET may involve any site, it predominantly affects bone, representing the third most common primary malignancy of bone following osteosarcoma and chondrosarcoma. It is most common in children and young adults with 80% of cases occurring before 20 years of age. This malignancy has a slight male predilection and affects Caucasians with a much greater frequency than African Americans. The histopathology is variable but typically includes a monomorphous round blue cell population of undifferentiated cells (ES) or cells with neuroectodermal features (PNET) arranged in sheets or nests. Immunohistochemical analysis shows the majority of cases are positive for CD99 (95%) and FLI-1 (90%) and a minority of cases highlight neuroendocrine markers. A translocation involving EWS on chromosome 22 and FLI-1 on chromosome 11 is seen in 90% of cases. The treatment for ES/PNET is surgery and chemotherapy with or without local radiation therapy. The prognosis of this family of malignant neoplasms is reported to be 65% at 5 years. Here, we describe two unusual cases with initial presentation in the gnathic bones prompting a diagnosis of ES/PNET.