

was performed with a clinical diagnosis of medication-related osteonecrosis of the jaw (MRONJ). The pathology revealed a high grade neuroendocrine cell tumor. Both cases were positive for neuroendocrine markers chromogranin, synaptophysin, and CD56, and stained negative for prostate specific antigen (PSA) and prostate specific acid phosphatase (PSAP). Both tumors demonstrated a proliferative index (Ki-67) of 60-70%. An extended panel of immunostains appeared to eliminate other entities from consideration.

Conclusions: Awareness of t-NECP is of importance to correctly diagnosis the entity, recognizing that tumor markers such as PSA and PSAP are negative, and standard serum markers for prostate carcinoma may be stable or show no increase with progression of disease. Neuroendocrine carcinoma in the setting of medication related osteonecrosis of the jaw in a patient with prostate carcinoma needs to be included in the differential diagnosis.

DRUG SCREENING OF ORAL CARCINOMA CELL LINES USING PLASTIC, MOUSE OR HUMAN TUMOR DERIVED MATRICES. MRS.

KATJA TUOMAINEN, DR. AHMED AL-SAMADI, DR. SAKHR AL-KUBATI, MRS. LAURA TURUNEN, DR. PIIA-RIITTA KARHEMO, DR. OUTI MONNI, MR. SWAPNIL POTDAR, PROF. TUULA SALO. UNIVERSITY OF HELSINKI

Objectives: Oral squamous cell carcinoma (OSCC) is the sixth most common cancer worldwide. Traditionally, cancer cell lines cultured in 2D are used to predict the efficacy of new anti-cancer compounds. However, this method has low predicting value for efficacy since more than 80% of the cancer drugs, which have promising effect in pre-clinical studies, fail in Phase II clinical trials. Our group has developed human matrix based product, Myogel, which is extracted from leiomyoma tissue. Our hypothesis is that Myogel represents better the in vivo condition compared with the 2D plastic wells, or even wells coated with mouse derived Matrigel®.

We selected 12 OSCC cell lines and 19 anti-cancer compounds, targeting mTOR and epidermal growth factor receptor (EGFR) signalling pathways. The High Throughput Drug Screening method with five different conditions were used: cells in 2D plastic wells; on top and within Matrigel® or Myogel. Additionally, the morphology of OSCC cells and EGRF location were studied using immunofluorescence staining and confocal microscope.

Findings: Cancer cells on top and within Myogel were less responsive to EGFR inhibitors compared to cells cultured in 2D plastic or Matrigel®. However, in case of mTOR inhibitors, similar efficacy of the drugs in all conditions was seen. The morphology of the carcinoma cells differed depending on the matrix. Within Matrigel, the cells formed isolated round-shaped organoids, whereas the cells within Myogel were stellate-shaped. Immunofluorescent staining revealed that in 2D and Matrigel, EGFR was located primarily on the cell membranes, while in Myogel, the staining was mainly in the cytoplasm.

Conclusions: Carcinoma cells showed different behaviours and responses to anti-cancer compounds depending on the testing conditions. Comparison between clinical data and our in vitro results are still needed to reveal the most reliable condition for cancer drug testing.

ORAL MANIFESTATIONS AID IN THE DIAGNOSIS OF COWDEN SYNDROME: ROLE OF AN ORAL DIAGNOSTICIAN. DR. PALLAVI PARASHAR^A, MS. MICHELLE SPRINGER^B, DR. ELIZABETH TOWNE^C. ^A UNIVERSITY OF ALBERTA, ^B UNIVERSITY OF COLORADO MEDICAL ONCOLOGY, ^C UNIVERSITY OF COLORADO SCHOOL OF DENTAL MEDICINE

Cowden Syndrome, also referred to as Multiple Hamartoma Syndrome or PTEN Hamartoma Tumor syndrome (PHTS), is an autosomal dominant disorder with a broad clinical spectrum and wide degree of penetrance. This rare disorder causes an increased predisposition to the development of numerous malignancies, and benign hamartomas and neoplasms. The oral manifestations have also been well documented and are present in nearly all affected individuals by the third decade of life.

Objective: To describe the role of an Oral Diagnostician in the preliminary diagnosis of Cowden Syndrome. We report a case of a patient who presented with pathognomonic oral signs of Cowden Syndrome. Upon further review of her medical and family history, she was referred to her family physician and genetic counselor where the diagnosis of Cowden syndrome was confirmed through genetic testing.

Findings: A 31 year old female presented to the dental clinic at University of Colorado for a routine dental evaluation. The patient was noted to have multifocal papules affecting the gingiva, tongue and buccal mucosa, and multiple papular skin lesions. She reported a history of a thyroid tumor and a family history of breast and uterine cancer. Based on the review of the medical history, family history and oral mucosal findings, a diagnosis of Cowden syndrome was considered. The patient was referred to her family physician and genetic counselor where the diagnosis of Cowden syndrome was confirmed through genetic testing (PTEN mutation). Additional clinical findings included macrocephaly, trichilemmomas and thyroid goiter.

Conclusion: The NCCN guidelines list multifocal or extensive oral papules as one of the major criteria in the diagnosis of Cowden Syndrome. The Oral Diagnostician can play a crucial role in the diagnosis. Early diagnosis of patients affected with Cowden syndrome can facilitate early screening, detection and management of benign and malignant neoplasms.

A UNIQUE PRESENTATION OF METASTATIC DISEASE IN A PATIENT WITH AN OCCULT HISTORY OF BREAST CARCINOMA. DR. SARAH AGUIRRE^A, DR. KRISTIN MCNAMARA^B, DR. JOHN KALMAR^A. ^A THE OHIO STATE UNIVERSITY, ^B OHIO STATE UNIVERSITY

Metastatic disease to the oral cavity is relatively rare and constitutes approximately 1% of all oral cavity malignancies. Skeletal involvement predominates over soft tissue presentations and the posterior region of the mandible is frequently affected. Pain, swelling and sensory alterations have been reported and may mimic periodontal or periapical disease or osteomyelitis. We present a case of a 63-year-old female with a complaint of progressive dyesthesia for three months. Panoramic and 3D imaging revealed widening of the PDL and loss of lamina dura affecting most of the mandibular teeth, which all tested vital. The patient's

medical history was significant for osteoporosis, but there was no history of anti-resorptive drug use. Upon examination, a gingival alveolar swelling was noted. Biopsy revealed high-grade adenocarcinoma, with immunohistochemical features most consistent with a breast primary. Subsequently, it was learned that the patient had a history of breast cancer, treated by total mastectomy of the left breast over three years previously with no previous evidence of metastases. The rarity of metastatic lesions to the jaw makes diagnosis particularly challenging. This case emphasizes the importance of assembling a thorough medical history as part of a complete patient work-up, especially in the presence of atypical symptoms or radiographic findings

THE TRANSITION OF TISSUE INHIBITOR OF METALLOPROTEINASE-4 TO -1 EXPRESSION MODULATES YAP/TAZ MEDIATED AGGRESSIVE PHENOTYPE IN LIPOSARCOMA. DR. MADHU SHRESTHA, DR. TOSHINORI ANDO, DR. CHEA CHAN-BORA, DR. IKUKO OGAWA, DR. MUTSUMI MIYAU-CHI, PROF. TAKASHI TAKATA. HIROSHIMA UNIVERSITY

Objectives: Liposarcoma(LS) is the most common soft-tissue sarcoma. The histological spectrum has a well-differentiated-liposarcoma(WDLS) and a more aggressive dedifferentiated-liposarcoma(DDLs). Advanced therapeutic strategies based on molecular mechanism are urgently needed, especially for DDLs. Previously, we reported that TIMP-1 (a member of tissue-inhibitor-of-metalloproteinase), with its receptor CD63 activates yes-associated protein (YAP) and transcriptional co-activator with PDZ binding motif (TAZ) to promote cancer cell proliferation. Aberrant YAP/TAZ activation in LS is reported, however, contribution of TIMP-1-YAP/TAZ axis in LS remains unclear. Intriguingly, TIMP-4 is known to share CD63 as TIMP-1, but its role in LS is unknown. Here we clarified the expression and function of TIMP-1 and -4 through YAP/TAZ regulation in LS.

Materials & Methods: Cell lines of WDLS(94T778) and DDLs(SW872) were used for in vitro experiments such as Western blotting, RT-PCR, cell-proliferation, migration and apoptosis assay.

Results: Database analysis showed high TIMP-1 expression in DDLs patients correlating with poor prognosis, while high TIMP-4 expression in WDLS patients with better prognosis. TIMP-1 knockdown in DDLs cells inactivated YAP/TAZ and suppressed cell-growth, migration, which was rescued by constitutively active form of YAP5SA. On the other hand, cell-growth and migration were significantly increased in TIMP-1 over expressing WDLS cells, which was suppressed by verteporfin (a YAP/TAZ inhibitor). TIMP-4 knockdown in WDLS activated YAP/TAZ, promoted cell-proliferation and migration, which was inhibited by verteporfin treatment or YAP/TAZ knockdown. Recombinant TIMP-4 showed opposite results in DDLs cells significantly. TIMP-4 CD63 binding inactivated YAP/TAZ in WDLS.

Conclusion: The switching of TIMP-4 to -1 expression during transition from a WDLS to a DDLs led to activation of YAP/TAZ and promoted cell-proliferation, migration, inducing poor prognosis. TIMP-1 and -4 as novel YAP/TAZ regulators may warrant future possibilities of targeting key molecules in development of diagnostic and therapeutic novelties in treating LS.

ARECA NUT EXTRACT ENHANCED M2-LIKE MACROPHAGE POLARIZATION AND FIBROBLAST ACTIVATION. DR. LIEN-YU CHANG^A, MR. PO-JU HSIAO^B, MS. CHIH-YUN LU^B, DR. YI-CHUN LIN^C, PROF. SHAN-LING HUNG^B, PROF. YU-LIN LAI^C. ^A NATIONAL YANG-MING UNIVERSITY, INSTITUTE OF ORAL BIOLOGY, DEPARTMENT OF DENTISTRY; ^B TAIPEI VETERANS GENERAL HOSPITAL, DEPARTMENT OF STOMATOLOGY; ^C NATIONAL YANG-MING UNIVERSITY, INSTITUTE OF ORAL BIOLOGY, ^C TAIPEI VETERANS GENERAL HOSPITAL, DEPARTMENT OF STOMATOLOGY; NATIONAL YANG-MING UNIVERSITY, DEPARTMENT OF DENTISTRY

Objectives: Areca nut chewing habit is popular in Taiwan and is closely related to oral squamous cell carcinoma (OSCC). Both activated fibroblasts expressing alpha-smooth muscle actin (α -SMA) and tumor-associated macrophages showing M2 polarization in stroma are supposed to be crucial in tumor progression. The purpose of the study was to examine the profile of stromal fibroblasts and macrophages in areca-associated oral cancer tissues, their *in vitro* effects of areca nut extract (ANE) and two common oral insults, nicotine (NT) and lipopolysaccharides (LPS), on primary oral fibroblasts and human macrophages were also investigated. The study was approved by institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan. Oral tissues were obtained with informed consent from patients undergoing routine surgical treatment.

Findings: Tissue sections showed that compared to the tumor-adjacent normal tissues (ANT), OSCC revealed a higher expression of pan-macrophage marker CD68, M2 markers CD163 and arginase-1 and activated fibroblast marker α -SMA, but not M1 marker CD86. In *in vitro* cell experiments, all of ANE, NT and/or LPS treatments could increase α -SMA expression and collagen production by oral fibroblasts. But only ANE treatment group, not NT or LPS group, enhanced the expression of M2 marker arginase-1 by macrophages. Furthermore, conditioned media acquired from macrophages (CM-Mac) of ANE treatment group increased the collagen production and IL-6 secretion by fibroblasts. CM-Mac of LPS treatment group also increased IL-6 secretion. Taken together, fibroblasts could be activated by ANE, NT and LPS, but only ANE could enhance macrophage M2-like polarization which in turn further increased fibroblast protein production.

Conclusions: Areca nut might compromise oral health by the setup of tumor-promoting microenvironment with local immune dysregulation via the enrichment of activated fibroblasts and M2-like macrophages.

INCREASED SOX2-POSITIVE CELLS IN BRAF (V600E) MUTATED AMELOBLASTOMAS. DR. JULIA YU FONG CHANG^A, DR. CHIH-HUANG TSENG^B, DR. PEI HSUAN LU^A, DR. YI-PING WANG^A. ^A NATIONAL TAIWAN UNIVERSITY HOSPITAL, ^B KAOHSIUNG MEDICAL UNIVERSITY HOSPITAL

Objective: SRY related HMG box gene 2 (SOX2) is a transcription factor expressed in embryonic and adult stem cells. SOX2 positive dental epithelial stem cells have been shown to give rise to all dental epithelial cell lineages. Increased SOX2 expressing cells has been reported in ameloblastic carcinomas than ameloblastomas, which might indicate SOX2 contributes to the pathogenesis of ameloblastic neoplasms. Recent and our