EDITORIAL

SIDE EFFECTS OF THE IMMUNE SYSTEM: LESSONS FROM TUBERCULOSIS-RELATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

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Immune reconstitution inflammatory syndrome (IRIS) is a recently described syndrome among human immunodeficiency virus (HIV)-infected patients attributable to the recovery of the immune system during antiretroviral therapy. A growing number of researches on this syndrome have been conducted in recent years, but IRIS in children has not been widely studied. We report the case of a 4.5 month-old, tuberculosis (TB)-HIV co-infected girl who developed IRIS two months after beginning antiretroviral and anti-TB medications. We moreover review the immunopathogenesis of TB-HIV coinfection and IRIS, with particular regard to TB-related IRIS.
EDITORIAL DENTISTRY SECTION

BISPHOSPHONATE AND OSTEONECROSIS OF THE JAW: THE ORAL SURGEON’S PERSPECTIVE

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Bisphosphonates (BPs) are an important class of drugs, useful in the treatment of some metabolic and oncologic skeletal diseases. BPs have shown a sure effectiveness in the treatment and in the palliative care of such pathologies; on the other hand, an avascular osteonecrosis of the jaws (B-ONJ = Bisphosphonate OsteoNecrosis of the Jaw) has recently been reported as an adverse effect not only of BP intravenous infusions, but also of their prolonged oral administration. B-ONJ normally follows a dental extraction or other surgical procedure in the oral cavity, but it also can develop spontaneously. In the latter case, some systemic risk factors, such as comorbidities and co-therapies or jaw anatomical conditions, can play a leading role in the onset of this pathologic condition. B-ONJ is an uncommon but potentially serious complication of BP therapy that can gravely affect the patient’s quality of life, producing significant morbidity. To date, no therapies are completely effective and predictable in the treatment of B-ONJ, therefore prevention should be strongly promoted by sharing knowledge in the involved medical community.
Ethyl pyruvate (EP) has been shown to have significant anti-inflammatory activities. Here, we explore the therapeutic effects of EP administration on tumor growth and metastasis in orthotopic implantation human gastric cancer models in severe combined immunodeficiency (SCID) mice. After SCID mice were treated with EP, the tumor growth and liver metastasis from gastric cancer were investigated and its possible molecular mechanisms were further studied. As a result, it was found that EP could inhibit tumor growth and liver metastasis of gastric cancer, and reduce tumor lymphangiogenesis indicated by lymphatic microvessel density (LVD) in gastric cancer and metastatic liver tumor. Also, EP decreased the expression of high mobility group box-B1 (HMGB1), receptor for advanced glycation endproducts (RAGE), vascular endothelial growth factor (VEGF) and membrane type-1 matrix metalloprotease (MT1-MMP) in gastric cancer and metastatic liver tumor, but it exerted no effect on expression of nuclear factor-kappa B (NF-κB). Taken together, we suggest that the new application of EP could be a therapeutic option in the treatment of gastric cancer and metastatic liver tumor.
Immunological and biochemical reactions associated with inflammation are elicited in response to a physical or immunological challenge. Early in inflammation there is mobilization and infiltration of neutrophils, mast cells and macrophages to the site of inflammation. These cells release pro-inflammatory compounds including cytokines, vasoactive peptides (e.g., histamine), and eicosanoids. The release of prostaglandin D2 (PGD2) and tryptase induced by anti-IgE, A23187 and compound 48/80 were studied using in vitro a good and valid model of human cord blood-derived mast cells (HCBDMC). Tryptase is a mast cell product and enhances vasopermeability with anticoagulant activities. In this study we measure the release of PGD2 and tryptase on mast cells activate by anti-IgE, calcium ionophore A23187, polybasic compound 48/80 (an agent containing a cationic region adjacent to a hydrophobic moiety, which works by activating G proteins) and IL-18. The generation of PGD2 was measured by radioimmunoassay. Release of PGD2 was detectable (after 12 h) following challenge with anti-IgE, A23187 and compound 48/80. Our data show that mature HCBDMC produce proinflammatory PGD2 following triggering with anti-IgE and with IgE-independent agonists, such as calcium ionophore A23187 and polybasic compound 48/80, while IL-18 was unable to stimulate the release of PGD2 or tryptase on HCBDMC. Although a great deal has been learned about the mediators produced by mast cells, the ultimate biologic function(s) of mast cells remains a mystery.
Previous studies have demonstrated that patients affected by Oral Lichen Plauns (OLP) show lower levels of salivary fibronectin when compared with normal controls. Similarly, tissue fibronectin expression is lost in epidermal basal layer and papillary dermis of OLP patients. To date, no data exist on the potential role of Plasma Fibronectin (PFN) in OLP pathogenesis, diagnosis and treatment. The objectives of the present study are: a) to determine the PFN levels in OLP patients; b) to evaluate a possible association between OLP clinical form and PFN levels; and c) to determine the PFN levels in relation to OLP signs and symptoms treatment. Twenty consecutive patients affected by OLP were enrolled. All patients were treated for eight weeks with topical clobetasol 0.05%. OLP signs and symptoms were scored before and after treatment. PFN level was determined by a nephelometric system. OLP signs and symptoms significantly improved after treatment. The mean levels of PFN were 31.84 mg/dL at the beginning and 26.76 mg/dL at the end of the study. The difference was not statistically significant (p=0.60). PFN in OLP patients remains in normal value range. OLP clinical form does not influence the PFN levels. Amelioration of symptoms and signs of atrophic-erosive and reticular OLP are induced by clobetasol treatment and the PFN seems not to interfere in the healing processes induced by topical corticosteroid. In contrast to what is observed in traumatic or diabetic wound healing, levels of PFN do not promote OLP lesion healing. PFN is not to be considered as a marker of OLP disease activity and its role in OLP pathogenesis still remains unclear.
PBS-1086, A Rel INHIBITOR OF NF-κB, AMELIORATES COLLAGEN-INDUCED ARTHRITIS IN MICE

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The family of nuclear factor-kappaB (NF-κB) transcription factors is intimately involved in the regulation of expression of numerous genes in the setting of the inflammatory response. Inflammation, cartilage degradation, cell proliferation, angiogenesis and pannus formation are hallmarks of the pathogenesis of both collagen-induced arthritis (CIA) in rodents and rheumatoid arthritis (RA) in humans. The aim of this study is to investigate the effect of PBS-1086, a Rel inhibitor of NF-κB, on the modulation of the inflammatory response in mice subjected to CIA in comparison to the effect of etanercept. CIA was induced in mice by an intradermal injection of bovine type II collagen (CII) emulsion and complete Freund’s adjuvant (CFA) at the base of the tail. On day 21, a second injection of CII in CFA was administered. Mice developed erosive hind paw arthritis when immunised with CII in CFA. Macroscopic clinical evidence of CIA first appeared as peri-articular erythema and oedema in the hind paws. The incidence of CIA was 100% by day 28 in the CII challenged mice and the severity of CIA progressed over a 35-day period with a resorption of bone. The histopathology of CIA included erosion of the cartilage at the joint. Treatment with PBS-1086 starting at the onset of arthritis (day 21) ameliorated the clinical signs at days 21-35 and improved histological status in the joint and paw. In addition, it also reduced the neutrophil infiltration which is a key mediator of RA. In this study, we demonstrate that PBS-1086 exerts an anti-inflammatory effect during chronic inflammation and ameliorates the tissue damage associated with CIA. The anti-inflammatory activities of PBS-1086 are comparable to those of etanercept treatment.
Delay in diagnosing oral squamous cell carcinoma (OSCC) can be still identified as a major cause of its high morbidity and mortality. To date, the early diagnosis for OSCC is mainly based on clinical oral examination and there is an urgent need for reliable markers; thus, advancements in molecular technologies has set the stage for investigating new markers, as well as new diagnostic matrices. The aim of the present study is to investigate the presence of proteomic signatures of OSCC in saliva and their use as potential biomarkers for early and non-invasive diagnosis. Saliva from 45 OSCC patients and 30 healthy controls was analysed by SELDI-TOF mass spectrometry and ProteinChip® technology. A supervised multivariate statistical analysis (Classification and Regression Tree – CART) was used to build models for discriminating between OSCC and controls, and between early (ES-OSCC) and late stage (LS-OSCC) cancers. The peptide with 8041 Da mass was 22-fold more expressed in OSCC, thus being a suitable potential biomarker. Classification and regression analysis allowed to build a model that was capable of correctly classifying all cancers and controls in an independent testing set, using the 8041 m/z peak as splitter. Eleven peaks were also differently expressed between ES-OSCC and LS-OSCC, but, basing on these differences, it was not possible to build an algorithm to predict tumour staging. These findings confirm that saliva proteome in OSCC patients is different from healthy controls and these variations might reflect different stages of disease progression and are worthy of further validation as diagnostic and prognostic biomarkers.
INTRA-ARTICULAR ULTRASOUND-GUIDED INJECTION OF SINOVIAL\textsuperscript{®} FORTE 1.6\% IN PATIENTS AFFECTED BY SYMPTOMATIC HIP OSTEOARTHRITIS: EFFECTIVENESS AND SAFETY IN A LARGE COHORT OF PATIENTS

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The aim of this prospective observational study is to assess the efficacy and safety profile of intra-articular Sinovial\textsuperscript{®} Forte 1.6\% administered under ultrasound-guidance in a large cohort of patients affected by symptomatic hip osteoarthritis (OA). Patients with symptomatic hip OA referred to our clinic in 2008-2010 received one 4 ml (2 vials) intra-articular injection of Sinovial\textsuperscript{®} Forte 1.6\% under ultrasound guidance. Patients were followed-up every 3 months for a total of 6 months and were offered an optional, additional injection at the 3-month follow-up visit if clinically justified. At each visit, pain scores [0-10 Visual Analogue Scale (pain VAS)], Lequesne index scores and NSAID intake were recorded. Adverse events (AEs) were recorded throughout the study. An effect size of 30\% and 50\% reduction in Lequesne index and Pain VAS scores was evaluated for each patient to ascertain the number of patients achieving partial remission of symptoms and functional impairment by the use of intra-articular hyaluronic acid in hip osteoarthritis. One hundred and fourteen patients completed the 6-month follow-up and received a total of 142 injections. A statistically significant reduction in Lequesne index score, VAS pain scores and NSAID consumption was observed at all time-points ($p < 0.05$). No systemic, severe or even moderate side effects were observed. Only 7 patients reported mild local reaction at the injection site, consisting of mild pain and localized warmth, which resolved spontaneously without any additional medication. This study provides evidence of the efficacy and tolerability of Sinovial\textsuperscript{®} Forte 1.6\% in the treatment of patients affected by symptomatic hip OA. Sinovial\textsuperscript{®} Forte may also offer economical benefits, owing to the reduction in NSAID consumption associated with this treatment. The percentage of patients achieving the effect size of 30\% and 50\% reduction in Lequesne index and pain VAS scores encourages the use of intra-articular hyaluronic acid in patients with hip osteoarthritis.
Periodontal diseases, the major public health problem of the oral cavity, are clinically characterized by inflammation of the periodontal connective tissue that ultimately induces the destruction of periodontal tissue and the loss of alveolar bone. In chronic periodontitis, as well as aggressive periodontitis, the anaerobic gram-negative bacterium *Porphyromonas gingivalis* (*P. gingivalis*) is implicated. The pathogenicity of *P. gingivalis* is exerted by a wide variety of factors, including lipopolysaccharides (LPSs). LPSs activate the innate immune response during Gram-negative bacterial infections through the Toll-like receptor 4 (TLR-4)/myeloid differentiation protein 2 (MD-2) complex. In this study, the expression of TLR-4, the cell growth, the cytokine release, and the nuclear factor-KB (NF-kB) transcription factor expression in response to LPS-*P. gingivalis* (LPS-G) were examined in Human Periodontal Ligament Mesenchymal Stem Cells (PDL-MSCs). The results obtained demonstrate that, in basal conditions, human PDL-MSCs express high levels of TLR-4. In inflammatory conditions mimicked by LPS-G challenge, the MTT assay carried out at different treatment times demonstrated the decrease of the cell growth. Moreover, the recognition of *P. gingivalis* components by TLR-4 culminated with the activation of secretion of inflammatory mediators such as: IL-6, IL-8 and CCL-20, and with the up-regulation of NF-kB, which was translocated into the nucleus. Our data intended to specify that TLR-4 expressed by PDL-MSCs is functional and plays a key role in inflammation.
HISTOLOGICAL EVALUATION OF PERI-IMPLANT SOFT TISSUES IN IMMEDIATELY LOADED IMPLANTS FEATURING DIFFERENT IMPLANT-ABUTMENT CONNECTIONS: A PRELIMINARY STUDY

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The aim of the present study is to evaluate the peri-implant soft tissues and the amount of inflammatory cells around two different implant-abutment connections (self-locking conical connection with platform switching and screwed connection with standard abutment and internal anti-rotational system). Histological analysis was made of 14 implants, 7 with self-locking Morse tapered connection (experimental group A) and 7 with screw-retained anti-rotational connection (control group B). Sixty days after non-functional immediate loading, peri-implant tissue biopsies were performed. In the samples taken from the experimental group the peri-implant connective tissue consisted of a greater density of collagen and fibroblasts compared to the connective tissue of the control group. The experimental group specimens showed less inflammatory infiltrate close to the self-locking tapered connection compared to the tissues around the screw-retained connection. The SEM observations showed less microgap in the self-locking conical connection than in the screw connections with standard abutment and internal anti-rotational system. The presence of connective tissue with few inflammatory cells and the absence of inflammatory infiltrate, in self-locking conical connection implants is due to the minimal size of the implant-abutment microgap that does not allow the passage of fluids and bacteria from the oral cavity to the implant thus preventing tissue inflammation.
INCIDENCE AND INTENSIVITY OF POSTOPERATIVE PAIN AND PERiapICAL INFLAMMATION AFTER ENDOdONTIC TREATMENT WITH TWO DIFFERENT INSTRUMENTATION TECHNIQUES

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BIOCOMPATIBILITY OF ROOT CANAL FILLING MATERIALS: DIFFERENCES BETWEEN VITALITY AND FUNCTIONALITY TESTS

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Biocompatibility of root canal filling materials is of great interest because they can come into permanent contact with the living periapical tissue, and induce mild or severe inflammatory responses. Usually biocompatibility tests only determine non-cytotoxic effects of dental materials, even if their functional interactions with cells also play a role in the host responses. The purpose of this study is to evaluate peripheral blood monocyte (PBM) vitality and functionality after contact with 5 different root canal filling materials: Thermafil (gutta-percha), Real Seal and Real Seal 1 (methacrylic resins), AureoSeal (MTA) and SuperSeal (EBA). Cellular vitality was determined by MTT test and cellular functionality by Chemiluminescence (CL) technique. Dishes of the materials were covered with cell culture medium (0.5 cm²/mL) and incubated for 24 h. The extracts were added to PBMs and the latter, after 2 h of incubation, were analysed by MTT and by Chemiluminescence (CL). All results are expressed as mean ± SEM. The group means were compared by analysis of variance. Results showed that SuperSeal and AuroSeal exhibited a moderate cytotoxic effect, while the toxicity induced by RealSeal, RealSeal 1 and Thermafil was lower. SuperSeal and AuroSeal induced a significant decrease of both oxidative burst and basal reactive oxygen species (ROS) production. RealSeal 1 caused a doubling of basal ROS production in respect to control. The results demonstrate that a low cytotoxic effect does not guarantee a total integrity of cellular functionality and more differences among biocompatibility of root canal materials can be detected when a functionality test is used.
ORAL FOCAL MUCINOSIS OF THE TONGUE: A RARE CLINICAL CASE

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Oral focal mucinosis (OFM) is a rare mucosal lesion of unknown etiopathogenesis. It is considered the oral counterpart of cutaneous focal mucinosis. From the anatomo-pathological point of view it is characterised by a focal degeneration of myxoid type of connective tissue. A literature survey revealed 50 reports of OFM cases worldwide. Here, we present an even more rare case with tongue involvement. Particular emphasis is placed on diagnostic-differential aspects of this kind of lesion, both from the clinical and the histopathological point of view, in respect to other manifestations of tongue mucosa.
LETTER TO THE EDITOR

RECURRENT DRUG-INDUCED INSULIN AUTOIMMUNE SYNDROME IN A PATIENT WITH PREMATURE OVARIAN FAILURE

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Insulin autoimmune syndrome (IAS) is characterized by hypoglycemic attacks, very high insulin levels and the presence of circulating autoantibodies to insulin in patients who have not been treated with exogenous insulin. Approximately half of patients with insulin autoimmune syndrome have a medication history preceding hypoglycemic events. We present the case of a young woman with premature ovarian failure who developed IAS initially after treatment with methimazole and several years later after captopril, and because of coexistent premature ovarian failure was classified as having autoimmune polyglandular syndrome (APS) type 3. Termination of methimazole and captopril treatment resulted in the disappearance of hypoglycemic episodes. We discuss diagnostic and treatment dilemmas associated with discovering and management of IAS and APS in this patient.
Flunisolide (6α-fluorine 11β, 16α, 17α, 21-tetrahydroxypregna-1, 4-diene-3.20-dione 16.17 acetonide) is a potent inhaled corticosteroid, as demonstrated by its anti-inflammatory activities. Clinical data have widely demonstrated that inhaled flunisolide administered twice daily is effective for the treatment of bronchial asthma. However, pharmacokinetic studies suggest that the high solubility rate of flunisolde in bronchial fluid reduces the residence time of the drug in the lungs to a few minutes. The aim of this study is to determine the concentration of flunisolide in lung tissue of rats after administration by inhalation at varying time periods. Male Wistar rats weighing approximately 300 g were divided into four groups and administered a single dose of 1 mg flunisolide via inhalation. Rats were sacrificed with the exposure to CO$_2$ either immediately or 3, 6, 12 hours after inhalation. The whole lung was then surgically removed and analysed for flunisolide concentration using gas chromatography. The mean concentration (2 standard deviation) of flunisolide detected in the lung tissue at 0, 3, 6 hours after inhalation were 66.4 (11.9), 48.6 (5.9), 42.7 (8.1) ng/mg of proteins, respectively. No flunisolide was detected after 12 hours in lung tissue. We conclude that flunisolide is retained for long duration (more than 6 hours) in lung tissue. This finding partially explains the mechanisms of action of the drug.
LETTER TO THE EDITOR

HEPATITIS C IS ASSOCIATED WITH HIGH LEVELS OF CIRCULATING N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE AND INTERLEUKIN-6

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To our knowledge, no study has evaluated N-terminal pro-brain natriuretic peptide (NTproBNP) together with interleukin-6 (IL-6) and interferon (IFN)-gamma serum levels in a large series of patients with hepatitis C virus (HCV) as possible markers of cardiac dysfunction. NTproBNP and IL-6 serum levels were valued in 55 HCV-patients, and in 55 sex- and age-matched controls. HCV-patients showed significantly higher mean NTproBNP and IL-6 levels than controls ($P = 0.001$); no significant difference was observed for IFN-gamma. By defining high NTproBNP level as a value higher than 300 pg/mL (that is used to rule out heart failure in patients under 75 years of age), 12% (6/49) of HCV-patients and 0 of controls had NTproBNP ($\chi^2; P = 0.012$). In conclusion, this study demonstrates high levels of circulating NTproBNP and IL-6 in HCV-patients. The increase of NTproBNP may indicate the presence of a subclinical cardiac dysfunction. Further prospective studies quantifying symptoms and correlating these with echocardiographic parameters are needed to confirm this association.
LETTER TO THE EDITOR

TWO CASES OF CERCARIAL DERMATITIS IN AN ITALIAN LAKE

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Cercarial dermatitis (also named Swimmer’s itch or Clam-digger’s disease) was first described about 80 years ago, but today its impact is increasing and it is considered an emerging disease. This represents a hypersensitive or allergic reaction to \textit{Trichobilharzia} spp, clinically characterized by initial erythema and cutaneous itching, followed by macular or papular eruptions, itching and occasionally diffuse erythema or urticaria. We report two cases of patients affected by a cercarial dermatitis after bathing in Lake Vico (Central Italy). We highlight these cases for the rarity of this dermatitis and its increasing prevalence, also in previously non-affected geographical areas, associated to a high level of social discomfort.
LETTER TO THE EDITOR

ASEPTIC ABSCESS: A REPORT OF TWO CASES

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An aseptic abscess (AA) is an auto-inflammatory disorder characterized by necrotic lymph nodes and internal organ abscesses, most frequently located in the spleen. Described herein are two cases of aseptic abscesses; one in a patient with Behçet’s disease and the other in a patient with mesenteric panniculitis.
LETTER TO THE EDITOR

THIRD MOLAR SURGICAL REMOVAL: A POSSIBLE MODEL OF HUMAN SYSTEMIC INFLAMMATION? A PRELIMINARY INVESTIGATION

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Accumulating evidence suggests that dental treatment is associated with systemic inflammation. We aimed to preliminarily study the impact of third molar removal on biomarkers of inflammation and oxidative stress. Ten consecutive subjects underwent the removal of third molars under local anaesthesia and provided blood samples before and 1, 7 and 60 days following therapy assessed for high-sensitivity serum concentrations of C-Reactive Protein (CRP), fibrinogen, white cell counts and a number of measures of oxidative stress (MDA, LOOH and FRAP). One week inflammatory response ensued with acute increases after 24 h of CRP (P<0.01), Fibrinogen (P<0.05) and white cell counts (P<0.05). Third molar removal may represent a useful model to investigate inflammation in humans.
LETTER TO THE EDITOR

SOFT-TISSUE HEALING AND IMPRESSION TECHNIQUE IN IMPLANT DENTISTRY:
A CASE REPORT

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The present clinical report describes a technique for aesthetic restoration of single dental implants in the anterior area. One objective of implant therapy in anterior areas is the achievement of an aesthetic result, which is highly dependent on the condition of the peri-implant soft tissue. A 22-year-old woman presented with right maxillary lateral incisor agenesis. An implant was placed, and a transfer impression technique carried out. The model was used to construct the custom abutment, provisional crown, and metal substructure. The metal substructure was covered with a waxed collar with the same emergence profile as the provisional restoration. The abutment and the provisional crown were placed, and after soft-tissue healing, an impression was taken using the waxed metal framework as coping. This final impression also registered and transferred the architecture of the soft peri-implant tissues. This clinical report describes an impression technique that accurately duplicates the peri-implant tissue profile. The final prosthesis is therefore shaped according to the interim prosthesis, for ideal contour and soft-tissue position. This technical procedure requires minimal chair time and is cost effective, as fewer components are used during the treatment.
GIANT CELL LESION OR LANGERHANS’ CELL HISTIOCYTOSIS OF THE MANDIBLE? A CASE REPORT

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Langerhans’ cell histiocytosis (LCH), formerly known as histiocytosis X, is characterized by cell proliferation. The leading clinical symptom of LCH within mandibular and maxillary bones is pain and it may resemble periodontal diseases, apical cysts, ameloblastoma, central giant cell granuloma, vascular malformation, osteomyelitis, bone metastasis and malignancies. In this paper we present the case of a mandibular histiocytosis misdiagnosed as a reparative giant cell granuloma at the first and as an aggressive giant cell tumor at the second biopsy. Definitive diagnosis was made only after examination of surgical specimens following hemimandibulectomy.