EDITORIAL

A CONTEMPORARY UPDATE ON PATHOLOGY REPORTING FOR URINARY BLADDER CANCER

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Providing the best management for patients with bladder cancer relies on close cooperation among uro-oncologists and pathologists. The pathologist is involved in the diagnosis and assessment of prognostic and therapeutic factors in bladder biopsies, transurethral resection (TUR) and cystectomy specimens. The pathologist must report accurately the key features using terms that are well understood by clinicians. Adequate clinical information is important to pathologists in deciding the best approach in handling and processing the surgical specimens.
Cancer cells invade surrounding tissues and metastasize to distant sites. Diet high in fat is a strong link to, and perhaps causes, a high incidence of tumours. Trans-fatty acid might impair the function and it could be involved in the development of cancer. Cholesterol is also strongly suspected to be involved in the development of tumours, therefore it is important for everyone to eat well, especially for people with cancer to prevent the body tissues from breaking down and helping to rebuild the normal tissue that may have been affected by the treatments. Factors secreted by adipocytes and macrophages such as TNF-alpha and other inflammatory proteins are involved in inflammation in cancer. In addition, MCSF which up-regulates adipocyte tissue is also important for the stimulation of fat cell proliferation and is expressed by human adipocytes. Many cytokines, such as IL-1, IL-6, IL-8, IL-32, IL-33 and MCP-1, are biomarkers for cancer and chronic diseases along with transcription factors NFkB and AP-1; these last two factors are important bioactive substances on the molecular mechanism of the control of genes which in turn affect cellular metabolism. In this paper we revisit the interrelationship between cancer and metabolism.
Yes-associated protein (YAP) has been implicated as an oncogene in multiple human cancers. In the present study, human gastric adenocarcinoma tissues of different grades (N=78) were collected and the mRNA and protein expression of YAP and phosphorylated YAP (p-YAP) in gastric adenocarcinomas were evaluated using immunohistochemistry, Real-time PCR and Western blot assays. Then, human gastric cancer SGC-7901 cells were stably transfected with lentivirus-mediated YAP small hairpin RNA (shRNA). The expression levels of YAP, proliferating cell nuclear antigen (PCNA) and metalloproteinase-2 (MMP-2) were detected and the effects of shRNA-mediated knockdown of YAP on cell proliferation and metastasis were assessed in gastric cancer cells. As a result, the expression of YAP was observed in 69.23% gastric adenocarcinoma tissues, elevating with the ascending order of tumor malignancy. Knockdown of YAP could down-regulated the expression of PCNA and MMP-2, and inhibit the proliferation and metastasis of gastric cancer cells. In conclusion, YAP is strongly expressed in gastric adenocarcinomas, and knockdown of YAP may inhibit gastric cancer cell proliferation and metastasis through down-regulation of PCNA and MMP-2 expression, suggesting that YAP represents an important therapeutic target in human gastric cancer.
Melatonin exhibits a wide variety of biological activity including antioxidant and anti-inflammatory effects. We have previously reported its protective effect on hepatic oxidative hepatic injury in burns. In this study, we investigated the role of nuclear factor kappa B (NF-kB) in melatonin-mediated protection against liver injury by using the burned-rat model. Melatonin (N-acetyl-5-methoxytriptamin, 10mg/kg, i.p.) was administered immediately and 12 hours after thermal skin injury. Hepatic NF-kB expression was determined by Western blotting. TNF-α level in liver homogenate was quantified using enzyme-linked immunosorbent assay (ELISA) kit. Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were determined to assess liver injury at the 24th hour after burns. Thermal skin injury caused significant elevation of hepatic NF-kB expression by 48%, TNF-α level by 55% and plasma AST and ALT activities by 2- and 3-fold, respectively, in comparison with normal control rats. Treatment with melatonin decreased significantly elevated hepatic NF-kB activity and TNF-α, maintaining the levels close to the control values Melatonin suppressed the elevation of plasma AST and ALT activities (p<0.001), which remained significantly increased compared to controls. In conclusion, thermal skin injury causes hepatic NF-kB activation that may mediate the release of hepatic TNF-α and contribute to liver damage. Melatonin protects against burn-induced hepatic injury as to a certain extent this effect may result from the suppression of NF-kB-mediated inflammatory response.
EFFECTS OF DEGRADABLE MG-ND-ZN-ZR ALLOY ON OSTEOBLASTIC CELL FUNCTION

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This study aimed to investigate the effects of a novel patented Mg-3Nd-0.2Zn-0.4Zr (weight %, JDBM) alloy on osteoblastic cell function, as these cells play an important role in bone repair and remodeling. The associated effects of the JDBM alloy on osteoblastic cell function involving cell adhesion, cell proliferation, and mineralization were investigated using scanning electron microscopy (SEM), MTT assay and ambramycin staining, respectively. At the same time, the in vitro degradation behavior of the JDBM alloy in cell culture medium was evaluated by the weight-loss method and SEM. Pure magnesium was used as control. The results showed that osteoblastic cells cultured on JDBM alloy samples manifested better cell adhesion, improved cell proliferation and increased mineralization ability, compared with cells seeded on pure magnesium samples. Our data indicate that the JDBM alloy has excellent bioactivity, improving the cell function of osteoblastic cells seeded on it.
Human pterygium is made up of chronic proliferative fibro-vascular tissue growing on the ocular surface. This disease exhibits both degenerative and hyperplastic properties. Some fibroangiogenic factors have recently been shown to play a potential role in fibrovascular diseases via the angiogenesis process. The aim of this study is to evaluate VEGF, TGF-β and PGE₂ expression in the epithelial, endothelial and stromal cells of human pterygium and normal conjunctiva in order to determine whether these factors participate in the development of pterygium. Ten specimens from patients with pterygium and two normal conjunctivas (cadavers) were analyzed by immunohistochemistry using specific antibodies against these growth factors. The technique used was ABC/HRP (Avidin complexed with biotinylated peroxidase). Immunoreactivity of VEGF was significantly increased in the epithelium, vascular endothelium and stromal cells in primary pterygium as compared with normal conjunctiva. A moderate expression of this growth factor in the pterygium was observed in the epithelial and stromal layers. On the contrary, immunolabeling of this growth factor in the human normal conjunctiva was weak. PGE₂ was strongly expressed in the epithelium of patients with pterygium, as in control conjunctival tissues, and the immunolabeling was moderate in the stroma from the same patients. Our results suggest that these growth factors may contribute to the progression of primary pterygium by increasing angiogenesis, thus leading to the formation of new blood vessels from the pre-existing vasculature. We conclude that VEGF, TGF-β and PGE₂ may be potential therapeutic targets in the treatment of this disease although proof of this evidence requires further studies.
We examined the effect of the protein kinase C-selective inhibitor AEB071 (sotrastaurin) on neutrophil functions in vitro. Pre-incubation with AEB071 at concentrations similar to those reached during in vivo therapy significantly reduced cell capacity to migrate toward three different chemo-attractants and to produce superoxide anions (O$_2^-$) in response to phorbol myristate acetate (PMA) or to N-formyl-methionyl-leucyl-phenylalanine (fMLP). AEB071 also significantly inhibited the O$_2^-$ overproduction induced by fMLP in neutrophils primed with tumor necrosis factor alpha (TNF-α) or granulocyte/macrophage-colony stimulating factor (GM-CSF). This inhibition was not linked to fMLP-receptor down-regulation since the drug had no effect on either fMLP-receptors or fMLP-induced CD11b membrane expression. When the activity of AEB071 was compared to that of the conventional protein kinase C (PKC) inhibitor Gö6850 (which, like sotrastaurin, inhibits classical and novel PKC isoforms), Gö6976 (an inhibitor of α and β PKC isoforms) and rottlerin (a prevailing δ PKC isoform inhibitor), AEB071 at an equimolar concentration of 3 μM (close to the maximum drug concentration reached in patients treated with AEB071) caused significantly more inhibition on both chemotactic response and superoxide production. These in vitro findings suggest that neutrophils may offer a cellular target for AEB071 activity in vivo.
Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway plays a crucial role in the formation and progression of many malignancies, and has been shown to be an important therapeutic target for cancer. In the present study, human gastric adenocarcinoma tissues of different grades (N=45) were collected. The protein expression of PI3Kp85α and phosphorylated AKT (p-AKT) was evaluated immunohistochemically in the biopsy samples. PI3K/AKT pathway was blocked by constructed recombinant small hairpin RNA adenovirus vector rAd5-PI3Kp85α (rAd5-P) used to transfect into human gastric cancer SGC-7901 cell line. The transfection efficiency of rAd5-P in SGC-7901 cells was observed under fluorescent microscope. The expression of PI3Kp85α, p-AKT, Ki-67 and matrix metallopeptidase-2 (MMP-2) was detected by Real-time PCR and Western blot assays. Cell proliferative activities and metastatic capabilities were determined by MTT and Transwell assays. As a consequence, the protein expression of PI3Kp85α and p-AKT was respectively observed in 80.0% and 82.2% gastric adenocarcinoma tissues, elevating with the ascending order of tumor malignancy. Targeted blockade of PI3K pathway decreased the expression of PI3Kp85α, p-AKT, Ki-67 and MMP-2, and inhibited the proliferative activities and metastatic capabilities of gastric cancer cells. In conclusion, PI3Kp85α and p-AKT were strongly expressed in gastric adenocarcinoma tissues, and targeted blockade of PI3K pathway may inhibit gastric cancer growth and metastasis through down-regulation of Ki-67 and MMP-2 expression. PI3K/AKT pathway may represent an important therapeutic target for gastric cancer.
MORPHOLOGICAL ANALYSIS AND INTERLEUKIN RELEASE IN HUMAN GINGIVAL FIBROBLASTS SEEDED ON DIFFERENT DENTURE BASE ACRYLIC RESINS

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The development of different types of materials with application in practice dentistry is an area of intense growth and research due to its importance in oral health. Among the diverse materials currently used in restoration or in dentures, the acrylic based resins have been widely employed. The release of toxic components and the changes on their physical and mechanical properties actually represent a goal of intensive research. In vivo analysis showed that the surface roughness of the acrylic resin represents a factor that could stimulate bacteria colonization and soft tissue inflammation. For this purpose, in this work, we have analyzed the cell response to acrylic based resins Ivoclar, Tokuso and Coldpack in basal conditions, unpollished, and after the polished procedure performed to reduce the surface roughness. Our in vitro results using human gingival fibroblasts (HGFs) showed a decrease of cell growth, evaluated by MTT assay starting at 24 h of incubation, in samples seeded on resins in basal conditions and after the polished procedure. This cell growth reduction was associated to evident morphological changes in unpollished materials. After 24 h of culture in presence of polished and unpollished resins a spontaneous release was present of pro-inflammatory cytokines such as Interleukin-6 (IL-6) and -8 (IL-8), which was higher in unpollished resins, indicating that the polished procedure, minimizing the cytotoxicity process, could contribute to reduce the gingival inflammation processes.
In humans, alcoholic liver disease is associated with hypergammaglobulinemia, particularly with high serum concentrations of IgA. Furthermore, alcohol consumption is associated with high concentrations of IgE and low concentrations of IgG. However, there is little experimental evidence to corroborate these observational findings. The objective of the present study was to investigate the potential short-term effects of alcohol administration on serum immunoglobulin concentrations in mice, and the potential influence of sex and strain on these effects. Eight mouse groups were defined by strain (Swiss vs C57BL/6), sex (male vs female), and experimental procedure (alcohol administration vs control diet). Alcohol was administered in a semi-liquid diet (6.5% v/v); control animals received an isocaloric semi-liquid diet. Immunoglobulin concentrations (IgE, IgA, IgM, IgG1, IgG2a, IgG2b, and IgG3) were measured at baseline and weekly thereafter for 4 weeks. Serum Th1 (interferon-gamma) and Th2 (IL-4 and IL-13) cytokines were measured at week 4. We found significant variations in baseline immunoglobulin concentrations depending upon mouse sex and strain. Alcohol administration was quickly followed by an increase in serum IgE concentrations in all experimental groups. IgE increase was correlated with serum IL-13 increase. In contrast, alcohol administration was not associated with significant changes in serum IgA and IgM concentration, and appeared to decrease IgG subclass concentrations. Alcohol effects on immunoglobulin concentrations were independent of mouse strain and sex. In conclusion, alcohol administration in mice had contrasting effects on IgE and other immunoglobulin classes. This experimental evidence confirms observational results in humans.
SUB-MICROMETRIC LIPOSOMES AS DRUG DELIVERY SYSTEMS IN THE TREATMENT OF PERIODONTITIS

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Periodontitis is a complex disease and bacterial infection is one of the most common factors involved in this disease. Current strategies for the local delivery of antibiotics do not allow a complete clearance of bacteria filling dentinal tubules and this limits their therapeutic efficacy. Therefore, there is a strong need for the development of new delivery strategies aimed at improving the efficacy of antibiotic therapy for periodontitis with special reference to their ability to penetrate into the tubules. The aim of the present study is to develop liposome-based delivery systems of sub-micron dimension, able to diffuse into the dentinal tubules. A further aim of the research is to develop a protocol for enhanced diffusion based on the use of magnetic liposomes and magnetic fields. Liposomes were produced by hydration of a pre-liposomal formulation. The vesicles were stabilised with PEG and their re-sizing was achieved by extrusion. Magnetite nanoparticles were synthesized inside the vesicles, i.e., the chemical reaction involving FeCl₂, FeCl₃ and NH₃ occurred within the core of the newly formed liposomes. Dynamic Light Scattering analysis was performed for size characterization. A mathematical model was implemented to predict the diffusion of the liposomes in dentinal tubules. Ex-vivo validation was performed on extracted human teeth. We produced PEGylated liposomes (average size 204.3 nm) and PEGylated magnetic liposomes (average size 286 nm) and an iron content of 4.2μg/ml. Through mathematical modelling, we deduced that sub-micrometer vesicles are able to penetrate into dentinal tubules. This penetration is considerably more effective when the vesicles are magnetized and subjected to an external magnetic field which accelerates their movement within the tubules. The liposome-based delivery systems developed by the present study are able to penetrate deeply into the tubules, sometimes reaching their terminal ends.
Sublingual immunotherapy with monomeric carbamylated allergoid (LAIS) is an effective and well tolerated treatment of respiratory allergy. The aim of the present study was to correlate the efficacy of two maintenance doses (1000 AU vs 3000 AU) of LAIS with the immunological modulation of allergen-driven Th1, Th2 and T regulatory cytokines produced in vitro by PBMCs, in patients suffering from mite allergic rhinitis. Forty-eight consecutive patients with mite allergic rhinitis were recruited. Patients were randomly assigned to group A (n=24) or group B (n=24), respectively receiving 1000 AU or 3000 AU weekly during one-year maintenance phase. Each patient was evaluated for rhinitis severity (ARIA protocol), and for drug consumption at the time of the inclusion and after 6 and 12 months of treatment. Patients were also asked to report the perceived severity of the disease and the tolerability of the treatment in a visual analogical scale (VAS). Before and at the end of the treatment allergen-driven release of cytokines by PBMCs in vitro was measured. After 1-year treatment, a statistically significant reduction of all clinical parameters was observed in all patients, associated with reduction of IL-4 and increase of INF-γ secreted in vitro by mite-challenged PBMCs. Notably, the group treated with the higher dose showed significantly better clinical and immunological results. The efficacy of LAIS is correlated to the immune modulation in a clear dose-dependent effect.
The aims of the present study are to define the prevalence of Pulmonary Hypertension (PH) in a cohort of Idiopathic Pulmonary Fibrosis (IPF) patients, to investigate any correlations between systolic pulmonary artery pressure (PAPs) and functional data, to evaluate clinical progress and to compare long-term survival in IPF patients with and without PH. A population of 126 IPF patients was recruited. A high prevalence of PH (39.7%, 50/126), evaluated by echocardiography on the basis of PAPs > 36 mmHg, was mainly observed in smokers and female patients. Regression analysis revealed a significant correlation between PAPs > 50 mmHg and DLCO/VA (p=0.0294). Mean PAPs was significantly greater one year after onset of PH (p=0.01). 11/21 patients with FVC <50% had a significant increase in PAPs one year after onset of PH (p=0.02). There was a highly significant difference between survival of IPF patients with and without PH (p=0.0001; hazard ratio = 3.56). This study revealed that PH has a high prevalence in patients with IPF and is associated with increased risk of mortality. Early diagnosis of IPF patients with pulmonary hypertension is important, so that they can be enrolled in waiting lists for lung transplant as soon as possible.
Alterations in hormone secretion and cytokine levels have been evidenced in many neoplastic diseases. In this study we have evaluated the circadian profile of growth hormone (GH), insulin-like growth factor-1 (IGF-1), interleukin-2 (IL2), melatonin (MEL) and cortisol (COR) serum levels in non-small cell lung cancer patients. Blood was sampled every 4 h for 24 h in 11 healthy (H) men (ages 35-53 years) and 9 men with stage 2, 3 or 4 non-small cell lung cancer (C) (ages 43-63 years). Serum GH, total IGF1, IL2, MEL and COR were measured and examined for group differences, trends, and rhythm characteristics. 24-h means were significantly higher in C234 vs H for GH, GH/IGF1, IL2 and COR, and lower for IGF1, but IL2 and COR were not different for C2 vs H. A linear regression across 4 groups (H, C2, C3, C4) found a positive trend for COR, GH, GH/IGF1 and IL2, and a negative trend for IGF1. A linear regression run between the 24-h mean levels of GH, IGF1, COR, MEL and IL2 in healthy subjects evidenced a statistically significant positive trend between MEL and GH (R=0.281, p=0.022) and in cancer patients showed a statistically significant negative trend between GH and IGF1 (R=0.332, p=0.01), COR and IGF1 (R=0.430, p=0.001), and a statistically significant positive trend between the 24-h mean of COR and GH (R=0.304, p=0.02). Rhythms in MEL and COR (peaks near 01:00h and 08:00h, respectively) indicated identical synchronization to the light-dark cycle for both groups. A circadian rhythm was detected in GH and GH/IGF1 for C23 and H, with IGF1 and IL2 non-rhythmic in any group. In conclusion, an increasing trend and progressive loss of circadian rhythmicity in GH and GH/IGF1, an increasing trend in cortisol and IL2, and a decreasing trend in IGF1 in C, reflect a complex chain of events that could be involved in progression of neoplastic disease. A therapeutic strategy needs to take into account circadian patterns and complex interactions of the multiple functions that characterize the hormone and cytokine levels in the frame cancer progression.
Malacoplakia is a rare inflammatory condition characterized by the accumulation of benign macrophages associated with pathognomonic Michaelis-Gutmann bodies (MGBs). It is usually found in the genito-urinary tract, and has been associated with immunocompromised states. In this short report, we present 5 patients with pulmonary nodules clinically suspicious for primary or metastatic lung cancer. The histologic examination of the surgical specimens revealed a nonspecific granulomatous chronic disease, and despite the paucity of classical MGBs, a pulmonary malacoplakia was suspected. In all cases the opportunistic pathogen Rhodococcus equi (R. equi) was identified by 16S rRNA gene sequence analysis, leading to the final pathological diagnosis of malacoplakia. We conclude that pulmonary malacoplakia associated with R. equi is a rare disease affecting also immunocompetent patients. The pathogenesis and the diagnostic problems are discussed. Since infection by R. equi is treatable, the importance of its early recognition should be emphasized.
The potential pathogenic effects of silica and carbon nanotubes (CNTs) on fibroblasts, macrophages/monocytes, and T cells were investigated. Human macrophage/monocytes were cultured and stimulated with silica, CNTs, or titanium particles. After adding human T cells to the stimulated macrophages/monocytes, the cells were added to cultured human fibroblasts. Upon microscopic examination, CNT stimulation after 24 hours showed centralization of macrophages/monocytes around the CNTs. Silica stimulation showed a significant increase of IL-1α and IL-1β in cultured medium, and an increased gene expression of CTGF in cultured fibroblasts at 1 hour, as well as an up-regulation of the COL1A2 gene at 24-hour time point. In addition to the same changes of IL-1α, IL-1β and the COL1A2 by silica, CNT stimulation showed an increase of IL-8 in cultured medium at 1-hour time point. Titanium stimulation yielded no significant changes. The results indicate a proinflammatory and/or profibrotic effect of silica and CNTs to cultured human cells including macrophages/monocyte, T cells and fibroblasts.
Allergic rhinitis (AR) is a very common childhood disease that is associated with a significant reduction in the patients’ quality of life. Its treatment combines educating the patients and their parents, immunotherapy and drug administration. However, even the best approach does not relieve the symptoms of a number of patients. Alternative therapies are particularly needed for children because the fear of adverse events frequently reduces parental compliance to the prescribed drugs, and immunotherapy is less easy to administer than in adults. In this prospective investigator-blinded study we evaluated whether children, with a documented history of seasonal grass pollen-related AR, benefit from nasal irrigation by assessing the effects on nasal signs and symptoms, on middle ear effusion and on adenoidal hypertrophy. We randomized children aged 5 to 9 years (median age 82 months) to normal saline or hypertonic saline (a 2.7% sodium chloride solution), administered twice-daily using a disposable 20 ml syringe, or no treatment. Nasal symptoms (rhinorrhea, itching, sneezing, nasal obstruction), swelling of turbinates, adenoid hypertrophy or middle ear effusion were assessed at baseline and after 4 weeks of treatment. Two hundred and twenty children (normal saline: 80; hypertonic saline: 80; no treatment: 60) completed the study. After four weeks, all the considered items were significantly reduced in the group receiving hypertonic saline (P <0.0001), whereas in the group receiving normal saline only rhinorrhea (P = 0.0002) and sneezing (P = 0.002) were significantly reduced. There was no significant change in any of the items in the control group. The duration of oral antihistamines was significantly lower in the children receiving hypertonic saline than in those treated with normal saline or in controls. No adverse events were reported and parental satisfaction and compliance with the procedure were globally very good, regardless of the solution used. Using our procedure, hypertonic saline is effective, inexpensive, safe, well tolerated and easily accepted by children with seasonal grass pollen-related AR and their parents. Our data suggest that nasal irrigation with hypertonic saline might be included in the wide spectrum of therapies recommended for grass-pollen AR.
Allergies are multifactorial diseases the onset of which depends also on genetic and environmental factors in early life. Thus, environmental factors can affect the immune response and modify lung development, thereby leading to asthma. The role of the factors used to date to predict asthma development is modest, and clinical criteria should always be considered in association with familiarity for atopy. The aim of this study is to evaluate the risk of asthma in a population with positive Skin Prick Test (SPT) (which is a reliable marker of atopy) to food allergens, regardless of clinical manifestations in the early years of life. The cohort of children enrolled in our study who had a positive SPT to food in the first three years of life had a prevalence of asthma after 7–14 years, double that of the general pediatric population. This prevalence increased significantly in patients with SPT positivity for food and inhalant allergens. We identified a correlation between the sensitization profile in children under the age of 36 months and the development of asthma during a period of 7–14 years. This study confirms that early sensitization is an important risk factor for the development of asthma, particularly in association with sensitization to inhalants, and that the persistence of food sensitization in school-age children and adolescents is associated to more severe asthma.
Leukocyte adhesion to endothelium plays a critical initiating role in inflammation. Berberine, an anti-inflammatory natural compound, is known to attenuate lipopolysaccharide (LPS)-induced lung injury and improve survival of endotoxemic animals with mechanism not fully clarified. This study investigated the effects of berberine on the LPS-induced leukocyte-endothelial cell adhesion both in vivo and in vitro.

We first established an animal model to observe the in vivo LPS-induced adhesion of leukocytes to the endothelium of venules in the lung tissue dose-dependently. Pretreatment of LPS-stimulated rats with berberine for 1 h reduced the leukocyte-endothelium adhesion and vascular cell adhesion molecule-1 (VCAM-1) expression in lung. Pretreatment of LPS-stimulated vascular endothelial cells with berberine also dose-dependently decreased the number of adhered THP-1 cells and VCAM-1 expression at both RNA and protein levels. Berberine was further confirmed to inhibit the nuclear translocation and DNA binding activity of LPS-activated nuclear factor-kappa B (NF-kappa B). These data demonstrated an additional molecular mechanism for the profound anti-inflammatory effect of berberine.
LETTER TO THE EDITOR

HAEMOPHAGOCYTIC SYNDROME ASSOCIATED WITH MUCORMYCOSIS INFECTION

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Several clinical forms of mucormycosis are recognized. The tendency of mucoraceous zygomycetes to invade the blood vessels often produces a disseminated infection. A case of a disseminated mucormycosis complicated by a haemophagocytic syndrome (HS) in a 32-year-old Caucasian male is reported in this article. Few cases of infection-associated HS (IAHS), involving infections caused by fungi, have been reported. In all the recorded cases, the fungal infection coexists with malignant lymphoma, immunodeficiency and a long-term steroid therapy for renal transplant or Crohn’s disease. This is the second described case of the HS due to mucormycosis.
LETTER TO THE EDITOR

NEOANGIOGENESIS IS REDUCED IN CHRONIC TENDINOPATHIES OF TYPE 2 DIABETIC PATIENTS

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In diabetes, the prevalence of tendon degeneration is increased. As neoangio genesis is impaired in several diabetic complications, the aim of this study is to evaluate the neovessel formation in tendinopathies. Patients aged > 55 years were selected, and divided into two groups: a) type 2 diabetic patients, and b) non-diabetic subjects. In both groups, those with ultrasound features of tendinopathy were included, and intratendinous vascularisation was estimated by means of Power Doppler. Ultrasound features of tendinopathy were observed in 104 diabetic subjects and in 221 controls. Neovascularisation, with higher Power Doppler scores, was found more frequently in controls, while lower Power Doppler scores were prevalent in diabetic subjects. In subjects with diabetes, tendinopathic features are significantly higher than healthy controls, while the prevalence of neovascularization inside tendons is less represented.
LETTER TO THE EDITOR

A CASE OF PERIOCULAR CONTACT DERMATITIS CAUSED BY CYPRESS ALLERGY

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Airborne contact dermatitis is a dermatological disease manifesting predominantly on the face, neck and arms, which is caused by volatile substances which settle on exposed skin. Although the diagnosis is not difficult, the finding of causative allergens and the exclusion of differential diagnoses are still lacking by the treating dermatologists.
LETTER TO THE EDITOR

CHRONIC IDIOPATHIC URTICARIA AND *HELCOBACTER PYLORI*: A SPECIFIC PATTERN OF GASTRITIS AND URTICARIA REMISSION AFTER *HELCOBACTER PYLORI* ERADICATION

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Chronic urticaria (CU) is defined as the occurrence of spontaneous wheals for a duration of more than 6 weeks and is the most frequent skin disease, with prevalence ranging between 15 and 25%, and is a seriously disabling condition, with social isolation and mood changes causing a significant degree of dysfunction and quality of life impairment to many patients. The main clinical features of CU are the repeated occurrence of transient eruptions of pruritic wheals or patchy erythema on the skin that last less than 24 hours and disappear without sequelae. CU is often defined as Chronic idiopathic urticaria (CIU) because the causes of CU remain unknown in the great majority (70-95%) of patients. Drugs, food, viruses, alimentary conservative substances or inhalant substances often seem to be involved in determining CIU skin flare. Despite a general agreement that bacteria infections and parasitic infestations can be involved in the pathogenesis of CIU, proven evidence of these relationships is lacking. The aim of the present study is to evaluate the prevalence of *Helicobacter pylori* (Hp) infection, and the extension and severity of gastritis in a group of CIU patients compared to controls and to evaluate the effectiveness of eradication of Hp on the CIU symptomatology, and the role of Hp infection in pathogenesis of CIU.
LETTER TO THE EDITOR

AMOXICILLIN AND CLAVULANIC ACID VS CEFTAZIDIME IN THE SURGICAL EXTRACTION OF IMPACTED THIRD MOLAR:
A COMPARATIVE STUDY

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The objective of this work is to compare the effectiveness and the side effects of two different drugs, amoxicillin and clavulanic acid vs ceftazidime, used as antibiotic prophylaxis in the surgical extraction of third molars and to demonstrate that the use of second choice antibiotic has no significant advantages in comparison with a first choice antibiotic. One hundred and seven patients with impacted third molar were selected and divided into two groups: amoxicillin and clavulanic acid were administered to group 1 and ceftazidime to group 2 for five days after surgery and we observed the postoperative period. The statistical analysis showed no differences between the two groups which lead to the conclusion that there is no indication to routinely administrate intramuscular second-choice antibiotic prophylactic therapy (ceftazidime) in case of surgical extraction of the third molar.
Vernal Keratoconjunctivitis (VKC) is a severe chronic bilateral inflammation of the ocular surface characterized by seasonal exacerbations. Long-term prognosis is generally good; however, 6% develop sequelae responsible for permanent visual impairment. Corneal involvement is almost always present, consisting of punctate keratitis, shield ulcers (3-11%) and late corneal neovascularization. In recent years, topical cyclosporine A preparations at 2% in oil or at 1% in polyvinyl alcohol, have been successfully proposed for long term VKC treatments. It has been previously proven that medical treatment is not always sufficient, especially when it is employed to treat shield ulcer plaques. In such conditions, surgery may be effective for avoiding long term complications such as amblyopia, strabismus, infections and corneal perforation. In this paper, we show the efficacy of surgical debridement by means of simple scraping associated with topical cyclosporine treatment for the management of vernal shield ulcers complicated with plaques.
Alopecia areata (AA) has been represented as a restricted T cell-mediated autoimmune disease. Several studies have shown that cytokines may play an important role in its pathogenesis although many pathways exist. We investigated cytokine (IL-2, IL-6, IL-12 and TNF-α) levels in peripheral blood mononuclear cell (PBMC) of 105 patients with different grade and duration of alopecia areata, to confirm that T-cell responses in AA is regulated via mechanisms of peripheral T-cell tolerance. We observed that IL-12 levels are higher for patients with bigger extensions and tend to increase according to the duration of the AA; TNFα, instead, is more related to the gender of the patients and to the duration. Therefore abnormalities in cytokines production, showed by our results, may suggest that T-cell responses in AA scalp are closely regulated via mechanisms of peripheral T-cell tolerance and therefore confirm that this disease has an immuno-pathogenesis. Our aim is to shed light upon the complexity of AA underlying mechanisms and indicate pathways that may suggest future treatments.
Bevacizumab is a humanized recombinant monoclonal antibody that blocks Vascular Endothelial Growth Factor (VEGF). Recently, its use has been related with osteneocrosis of the jaws (ONJ), a disease showing a histological pattern similar to bisphosphonate-related ONJ. The aim of this study is to describe an ONJ case-report following bevacizumab chemotherapy without bisphosphonate therapy. We monitored ONJ development associated with the use of bevacizumab in a 47-year-old male with primitive adenocarcinoma of the parotid gland. Our results could suggest a possible correlation between the eruption of the lower third molar tooth and ONJ development following bevacizumab therapy. Clinicians should be aware of the potential risk of bevacizumab-related ONJ complication; moreover, since there are no effective therapeutic protocols for ONJ treatment, it is very important that patients develop good oral hygiene habits and undergo regular dental status evaluation by dentists.
LETTER TO THE EDITOR

IMPACT OF ORAL IMMUNOTHERAPY ON QUALITY OF LIFE IN CHILDREN WITH COW MILK ALLERGY: A PILOT STUDY

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Quality of life is negatively affected in children with food allergy. Oral immunotherapy is an approach to food allergy that leads to patient desensitization by administering gradually increasing amounts of a given food allergen. The aim of this pilot study is to evaluate how oral immunotherapy affects quality of life in children allergic to cow milk proteins. Thirty children (aged 3-12 years) with cow milk allergy were recruited. Their parents were provided with a validated disease specific quality of life questionnaire (the food allergy quality of life questionnaire – parent form, FAQLQ-PF) before and again 2 months after completing an oral immunotherapy protocol with cow milk. A significant improvement in all the investigated domains - emotional impact, food anxiety and social and dietary limitations - was found. The separate analysis of the different age groups demonstrated that the emotional impact and the food-related anxiety improved in children older than 4, while the social domains improved in each age group. In this pilot experience, oral immunotherapy significantly improves quality of life in children with cow milk allergy. The improvement seems particularly evident in children over 4 years old, who are most likely to benefit from the oral immunotherapy approach. Further placebo-controlled studies are needed to confirm these preliminary results.
LETTER TO THE EDITOR

CO-EXPRESSIO N OF MULTIPLE CYTOKINES AND THEIR RECEPTORS IN PRIMARY CLEAR CELL SARCOMA OF THE PUBIC BONE WITH FEATURES OF A SMALL ROUND CELL TUMOR

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We present the case of an 81-year-old man with primary clear cell sarcoma (CCS) of the pubic bone with an associated aggressive clinical course. The patient’s laboratory tests showed marked leukocytosis, elevated levels of C-reactive protein and multiple cytokines, including interleukin-6 (IL-6) and granulocyte colony-stimulating factor (G-CSF). Histological examination showed monomorphic small cells predominantly arranged as a diffuse sheet with morphological features of a small round cell tumor (SRCT). Immunohistochemical staining indicated that the tumor cells were positive for HMB45, S100, Melan A, IL-6, IL-6 receptor, G-CSF, and G-CSF receptor and negative for cytokeratin (AE1/AE3) and epithelial membrane antigen. To the best of our knowledge, this is the first case report of aggressive primary CCS of the pubic bone with features of SRCT showing the production and co-expression of multiple cytokines and their receptors. Thus, we suggest that proliferation through an IL-6- and G-CSF-associated autocrine mechanism may play an important role in the aggressive clinical course and poor prognosis of some CCSs showing features of SRCT.
LETTER TO THE EDITOR

ANTIBACTERIAL ACTIVITY OF VARIOUS ANTIBIOTICS AGAINST ORAL STREPTOCCI ISOLATED IN THE ORAL CAVITY

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A total of 550 oral streptococci: 270 Streptococcus mitis, 110 Streptococcus sanguis, 90 Streptococcus anginosus, 50 Streptococcus mutans, 30 Streptococcus salivarius, were isolated from dental plaque and gengival crevices of patients and tested for their susceptibility to 12 β-lactam antibiotics and to 5 non-β-lactam antibiotics, using the microdiluition method. Overall, a reduced susceptibility to penicillin was recorded in 13.4% of cases. The percentage of strains resistant to penicillin appeared significantly higher in S. mitis (24%) than in S. sanguis (19%), in S. mutans (14%) and in S. salivarius (10%). No levels of penicillin resistance were shown by 90 strains of S. anginosus. In susceptibility test to antibiotics, imipenem was the most active molecule tested, confirming its general good activity against oral streptococci. Also third generation cephalosporins such as ceftriaxone and fourth generation cephalosporins such as cefepime, showed good activity. Chinolones, glycopeptides and rifampicin confirmed a good activity against oral streptococci.
LETTER TO THE EDITOR

Vav1 HAPLOINSUFFICIENCY IN A COMMON VARIABLE IMMUNODEFICIENCY PATIENT WITH DEFECTIVE T-CELL FUNCTION

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Common variable immunodeficiency (CVID) is a primary immune disorder characterized by impaired antibody production, which is in many instances secondary to defective T cell function (T-CVID). We previously identified a subset of T-CVID patients characterized by defective expression of Vav1, a guanine nucleotide exchanger which couples the T-cell antigen receptor to reorganization of the actin cytoskeleton. Here we have addressed the possibility that an intrinsic defect in the Vav1 gene might underlie the reduction in Vav protein observed in T cells from these patients. We report the identification in one T-CVID patient of a heterozygous deletion in Vav1. The gene deletion, spanning exons 2-27, accounts for the reduction in Vav1 mRNA and protein in T cells from this patient. The disease-related pedigree of this patient suggests a de novo origin of the Vav1 deletion. The findings highlights Vav1 as an autosomal dominant disease gene associated with CVID with defective T-cell function.