EDITORIAL

ITALIAN SURVEY ON THE USE OF ANTI-INFLAMMATORY DRUGS IN OSTEOPATHY

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Osteoarthritis (OA) is the most common painful arthritic disease in adults, causes severe disability and worsens the quality of life of the patients. The aim of this survey, carried out on 147 Italian orthopedic doctors who attended an ISIAT (International Symposium Intra Articular Treatment) educational course in Barcelona, was to investigate some aspects of daily clinical practice in the management of OA: the most used pharmacological treatments, compliance to the most important Guidelines, the advantages of COXIBs in this setting and pharmacoeconomic aspects. The main results of this survey are: a) inflammation has become the main target in OA; b) Guidelines are a useful and valid tool for daily clinical practice; c) acetaminophen is no longer a valid therapeutical option for OA patients; d) anti-inflammatory drugs (NSAIDs and COXIBs) have a primary role in the management of OA, due to their dual activity (anti-inflammatory and analgesic); e) selectivity of COXIBs for COX-2 is very important; f) within the COXIB class, the therapeutic value of etoricoxib has been widely recognized, especially in terms of safety and cost/benefit ratio.
Phosphatases are important enzymes in a variety of biochemical pathways in different cells which they catalyze opposing reactions of phosphorylation and dephosphorylation, which may modulate the function of crucial signaling proteins in different cells. This is an important mechanism in the regulation of intracellular signal transduction pathways in many cells. Phosphatases play a key role in regulating signal transduction. It is known that phosphatases are specific for cleavage of either serine-threonine or tyrosine phosphate groups. To date, numerous compounds have been identified. This paper reviews the classification, roles and pharmacological of protein serine/threonine phosphates.
VITILIGO: SYMPTOMS, PATHOGENESIS AND TREATMENT

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Vitiligo is an acquired cutaneous disorder of pigmentation, with an incidence of 0.5% to 2% worldwide. There are three major hypotheses for the pathogenesis of vitiligo that are not exclusive of each other: biochemical/cytotoxic, neural and autoimmune. Recent data provide strong evidence supporting an autoimmune pathogenesis of vitiligo. As vitiligo can have a major effect on quality of life, treatment can be considered and should preferably begin early when the disease is active. Current treatment modalities are directed towards stopping progression of the disease and achieving repigmentation. Therapies include corticosteroids, topical immunomodulators, photo(chemo)therapy, surgery, combination therapies and depigmentation of normally pigmented skin. It seems that traditional Chinese medicine could be more effective than the current treatment for vitiligo.
Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory metabolic disease that is caused by mutations in the MVK gene. Patients with MKD typically have an early onset in infancy. MKD is characterized by recurrent episodes of high fever, abdominal distress, diffuse joint pain, and skin rashes. In a subset of patients, MKD is also associated with elevated serum immunoglobulin D (IgD) levels (hyperimmunoglobulinemia D syndrome, HIDS). The clinical phenotype of MKD varies widely and depends on the severity of the impaired mevalonate kinase activity. Complete impairment results in the severe metabolic disease, mevalonic aciduria, while a partial deficiency results in a broad spectrum of clinical presentation, including HIDS. The precise molecular mechanisms behind the elevated serum IgD levels and inflammation that occurs in MKD remain unknown. Children who exhibit symptoms of MKD should be tested for mutations in the MVK gene. However, the complexity of MKD often results in delays in its definitive diagnosis and the outcome in adult age is not completely known. Therapeutic options for MKD are based on limited data and include non-steroidal anti-inflammatory drugs, corticosteroids, and biological agents that target specific cytokine pathways. In recent years, some studies have reported promising results for new biological drugs; however, these cases have failed to achieve satisfactory remission. Therefore, further studies are needed to understand the pathogenesis of MKD and identify innovative therapeutic tools for its management.
EDITORIAL

RHINOSINUSITIS AND ASTHMA: A VERY LONG ENGAGEMENT

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Upper and lower airways may be considered as a unique entity, interested by coexisting inflammatory processes that share common etiopathogenic mechanisms. Previous studies have strongly demonstrated a relationship between rhinosinusitis and asthma. This has led to the introduction of the concept of “united airways”, which has also been included in the WHO document Allergic Rhinitis and its Impact on Asthma (ARIA); this concept has important consequences also on the treatment of these disorders. To better summarize the evident connection between upper and lower airway disease we decided to describe it as a multilayered construction, each level pointing out more deeply the relationship between these entities.
PATHOLOGY OF UPPER TRACT UROTHELIAL CARCINOMA WITH EMPHASIS ON STAGING

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Classification of upper tract urothelial preneoplastic and neoplastic lesions mirrors that of the urinary bladder, with all lesions of the bladder urothelium being possible in the upper tract and vice versa. There are three major groups of non-invasive urothelial neoplasms: flat, papillary, and inverted. These three groups share a similar morphological spectrum of intraurothelial changes, ranging from hyperplasia to dysplasia to carcinoma in situ. However, they differ in terms of architectural growth pattern compared to the surrounding non-neoplastic mucosal surface. Infiltrating urothelial carcinoma is defined as a urothelial tumor that invades beyond the basement membrane. Unlike in non-invasive papillary urothelial neoplasms (pTa), the role of histologic grade in pT1 and higher stage tumors has been suggested to be of only relative importance. The vast majority of tumors of the upper urinary tract are urothelial carcinoma. More commonly seen, however, are foci of squamous differentiation and, less frequently, glandular differentiation. Pure urothelial carcinomas also display a wide range of variant morphologies, and recognition of these morphologies is important for diagnosis, classification, and prognosis.
Atherosclerosis is an inflammatory disease and hyperlipidaemia is one of the main risk factors for aging, hypertension and diabetes. Variance in plasma LDL cholesterol concentration may be associated with differences in cardiovascular disease risk and high levels of lipids are associated with increased risk of developing atherosclerosis. Macrophages, which generate pro-inflammatory cytokines, mainly interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-alpha), are deeply involved in atherosclerosis, as well as mast cells which generate several cytokines, including IL-6 and IFN-gamma, and chemokines such as eotaxin, MCP-1 and RANTES involved in monocyte recruitment and differentiation in the arterial wall. In addition, mast cells participate in lipid retention and vascular cell remodeling, and are mediators of innate and adaptive immunity during atherosclerosis. Mast cells which accumulate in the human arterial intima and adventitia during atherosclerotic plaque progression, release vasoactive and angiogenic compounds, and pro-inflammatory mediators, such as arachidonic acid metabolites, histamine, cytokines/chemokines, platelet activating factor (PAF) and proteolytic enzymes. Mast cells can be activated by pro-inflammatory stimuli, including cytokines, hypercholesterolemia, and hyperglycemia, and trigger the endothelial expression of adhesion molecules such as P-selectin, vascular cell adhesion molecule-1 (VCAM-1) and chemokines which mediate the recruitment and adhesion of leukocytes. The participation of mast cells in atherosclerosis is still an enigma and it may be of therapeutic interest to clarify this process.
Arabinoxylan rice bran (MGN-3/Biobran) has been shown to be a potent biological response modifier (BRM) that activates different arms of the immune system, including dendritic cells (DCs), which prime CD4+ helper T-cell responses. The present study explores the ability of MGN-3-activated DCs to prime CD8+ T cells and examines the mechanisms underlying its effect. Human monocyte-derived DCs were treated with MGN-3 (20 and 40 μg/ml). Results indicate that treatment with MGN-3 caused DCs to prime higher granzyme B-expressing CD8+ T cells. Tumor lysate-pulsed MGN-3 DC also increased tumor cell killing compared to DC-stimulated CD8+ T cells. This was associated with: i) increased expression of DEC-205 in MGN-3-activated DCs in a dose-dependent manner; and ii) MGN-3 induced significant production of Type III interferon, IL29, but not Type I IFNs α and β. These results suggest that MGN-3 is a potent natural adjuvant that efficiently activates DCs and may therefore be useful for mounting an efficient immune response against infections and cancer.
IMMUNOPATHOLOGICAL AND ANTIMICROBIAL EFFECT OF BLACK PEPPER, GINGER AND THYME EXTRACTS ON EXPERIMENTAL MODEL OF ACUTE HEMATOGENOUS PYELONEPHRITIS IN ALBINO RATS

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Recent studies showed prominent antimicrobial activity of various plant extracts on certain pathogenic microorganisms, therefore we prepared crude aqueous extracts of black pepper, ginger and thyme and carried out an \textit{in vitro} study by measuring antimicrobial activity of these extracts using the agar well diffusion method. An \textit{in vivo} study was carried out on 50 adult healthy male albino rats which were divided into 5 groups, 10 rats each. Group 1: negative control group which received saline solution intragastrically daily; Group 2: Positive control group, injected with mixed bacterial suspension of \textit{S.aureus} and \textit{E.coli} as a model of pyelonephritis, then received saline solution intragastrically daily; Group 3: injected with the same dose of mixed bacterial suspension, then received 100 mg/kg/day black pepper extract intragastrically; Group 4: injected with mixed bacterial suspension then received 500 mg/kg/day ginger extract intragastrically. Group 5: injected with mixed bacterial suspension then received 500 mg/kg/day thyme extract intragastrically. All groups were sacrificed after either 1 or 4 weeks. Serum and blood samples were collected for lysozyme activity estimation using agarose lysoplate, measurement of nitric oxide production, and lymphocyte transformation test as well as for counting both total and differential leukocytes and erythrocytes. Kidney samples were tested histopathologically. Both \textit{in vivo} and \textit{in vitro} results confirm the efficacy of these extracts as natural antimicrobials and suggest the possibility of using them in treatment procedures.
High mobility group box 1 (HMGB1) has been proved to be implicated in a variety of cell physiological and pathological behaviors including immune response, inflammation and cancer. Accumulating evidence suggests that HMGB1 plays a critical role in the development and progression of multiple malignancies. However, the clinical significance and prognosis of HMGB1 expression in some cancers remain controversial. The present study aimed to investigate whether overexpression of HMGB1 is an independent prognostic factor in patients with gastric cancer. The correlation of HMGB1 expression with clinicopathologic characteristics and prognosis was assessed by immunohistochemical assay through tissue microarray procedure in 50 primary gastric cancer cases. Our results indicated that the positive expression of HMGB1 was significantly increased in the nucleus of gastric cancer tissues compared with the adjacent non-cancerous tissues (ANCT) ($64.0\%$ vs $44.0\%$, $P=0.025$), but was not linked to the clinicopathologic features, including the TNM stage ($P=0.533$) and metastatic lymph node ($P=0.771$), in patients with gastric cancer. Kaplan-Meier and log-rank analysis demonstrated that overexpression of HMGB1 did not exert significant impact on the overall survival of patients with gastric cancer ($P=0.805$). Furthermore, Cox regression analysis showed that high HMGB1 protein expression did not represent an independent risk factor for patients with gastric cancer ($P=0.677$). Taken together, our findings suggest that high expression of HMGB1 is not correlated with the clinicopathologic characteristics of gastric cancer, and can not serve as an independent prognostic biomarker for patients with gastric cancer.
Chemokines have been shown to play a critical role in tumor development and progression. However, little is known about the function and molecular mechanisms of CXCR6 in multiple malignancies. In the present study, we aimed to investigate the role of CXCR6 in human hepatocellular carcinoma (HCC). The expression of CXCR6 was examined by immunohistochemical assay using a tissue microarray procedure. A loss-of-function experiment was performed to explore the effects of lentivirus-mediated CXCR6 shRNA (shCXCR6) on cell proliferation and invasive potential by MTT and Transwell assays in HCC cell line (SMMC-7721). It was found that the expression of CXCR6 protein was significantly increased in HCC tissues compared with that in adjacent non-cancerous tissues (ANCT) (63.04% vs 36.96%, P=0.019), and correlated with the lymph-vascular space invasion in HCC patients (P=0.038). Knockdown of CXCR6 repressed cell proliferation and invasion of HCC cells followed by the down-regulation of vascular endothelial growth factor (VEGF). Taken together, our findings show that high expression of CXCR6 is positively associated with distant invasion of HCC patients, and blockade of CXCR6 signaling suppresses the growth and invasion of HCC cells through inhibition of the VEGF expression, suggesting that CXCR6 may represent a promising therapeutic target for the treatment of HCC.
Clinical manifestations of respiratory syncytial virus (RSV) infection vary from minimal disease to severe acute bronchiolitis. The structural complex of TLR4/CD14 participates in the virus recognition as a component of natural immune response. Genetic variations of TLR4/CD14 may explain great variations in disease severity. The aim of this study was to investigate the possible role of polymorphisms of TLR4, Asp299Gly and Thr399Ile and CD14, C-159T and C-550T in the development of RSV bronchiolitis. Our study included two groups of Greek infants and young children (A and B). Group A consisted of 50 infants ≤2 years of age hospitalised with bronchiolitis and group B of 99 previously healthy children aged 4-14 years (control group) with a free past medical history. RSV was identified by PCR of genetic material that was extracted from nasopharyngeal samples collected from all patients. Blood samples were used to extract DNA and by using the PCR-RFLP method we performed TLR4 and CD14 genotyping. We found no association between TLR4 polymorphisms (Asp299Gly and Thr399Ile) and the development of acute bronchiolitis. For CD14 polymorphisms, a positive association was found between the C-159T and the development of bronchiolitis (p=0.05) but not for the other loci. There were no differences detected in the frequencies of the four polymorphisms studied among infants with RSV and non-RSV bronchiolitis. It is concluded that protein CD14 may have a functional role in the viral conjunction to the structural complex TLR4/CD14. The association between the polymorphism C-159T and the manifestation of disease found in our study points out that the severity in the development of acute bronchiolitis is not specified exclusively by the pathogen, but the immune response of the host also plays a significant role. More extensive multicentric studies need to take place, in order to lead to safer conclusions.
Pathological acid reflux is a common event in patients afflicted with head and neck squamous cell carcinomas (HNSCCs), known to play a role in HNSCC etiology and contribute to complications after surgery or during radiation and chemotherapy. Antacid medications are commonly prescribed in HNSCC patients as part of their cancer treatment, and consist of two classes: histamine 2 receptor antagonist class (H2RA, with cimetidine as its prototypical drug) and proton pump inhibitors class (PPI, with omeprazole as its prototypical drug). Clinical evidence revealed a significant survival benefit of antacid usage in a large cohort of HNSCC patients treated in our Otolaryngology Department, with a median follow-up of over 5 years. Therefore, we postulate that one mechanism by which antacid intake enhances patient survival could involve modulation of tumor cell adhesion to endothelium, critical in the initiation of the metastatic dissemination. This study investigates the potential physical interactions between cimetidine and omeprazole with the endothelial E-selectin (E-sel) and its ligand sialyl Lewis X (sLe\(^X\)) using a molecular visualization energy-based program (AutoDock). Docking results were further analyzed with the PyMOL program, which allowed for measurements of the distances between the drugs and the closest interacting atoms or residues on E-sel and sLe\(^X\) molecules. Our model predicts that omeprazole displays a stronger interaction with E-sel than cimetidine, as extrapolated from the calculated overall binding energies. However, the shorter distances existing between interacting atoms in the proposed E-sel/cimetidine complex are suggestive of more stable interactions. Neither antacid/E-sel complex overcame the stronger Autodock-calculated sLex/E-sel interaction, suggesting competitive inhibition was not involved. This study provides the first in silico evidence of omeprazole and cimetidine ability to bind to adhesion molecules involved in tumor dissemination, underlining their therapeutic potential in the HNSCC clinical management.
"FoxP3 HUNTING" DURING INFECTION WITH FRANCISELLA TULARENSIS

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Francisella tularensis is a Gram-negative intracellular bacterium that can cause acute disease in mouse models of infection when administered via the inhalational route. The immune response to a pulmonary infection is typified by an initial lack of pro-inflammatory cytokines, followed by hypercytokinemia prior to host death. It remains unclear what causes this delay in the host immune response. In this study we determine the presence of FoxP3 regulatory T cells in the lung, liver and spleen following intranasal infection with F. tularensis SCHU S4. In the lung, the site of initial infection, there is an increase in FoxP3+ cells during the first few days of infection and a notable absence of these cells at the point of cytokine storm and death (day 4 post-infection). This coincides with a decrease in the anti-inflammatory cytokine TGF-β and increases of chemokines MIP-1α, MIP-1β and RANTES. In our model, we also observed an overall decrease in the number of regulatory T cells in the spleen, which was not as evident in the liver. Overall, this data suggests that early on in an acute F. tularensis SCHUS4 infection regulatory T cells contribute to a dampening of the pro-inflammatory response, allowing for bacterial replication and spread.
MANAGEMENT AND TREATMENT OF ANAPHYLAXIS IN CHILDREN: STILL TOO LOW THE RATE OF PRESCRIPTION AND ADMINISTRATION OF INTRAMUSCULAR EPINEPHRINE

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Despite it being well known that anaphylaxis is a severe life-threatening reaction requiring prompt management and treatment, this entity is still under-recognized and not correctly managed, above all in children. The aim of this study was to analyze the most frequent features of anaphylaxis in a pediatric population (n=65 patients) and to identify factors predicting more severe reactions. Among the 70 recorded episodes, food was the main culprit of anaphylaxis, and patients with a positive history for allergic asthma had more severe episodes (P=0.008). A self-injectable adrenaline was used only in 2 of the 70 episodes and none of the 50 episodes managed in the Emergency Department was treated with intramuscular adrenaline. Only 10/65 patients (15%) had a prescription for an auto-injector prior to the first episode of anaphylaxis. The retrospective analysis of the risk factors potentially requiring an epinephrine auto-injector prescription before the first anaphylactic episode, showed that of the 55 patients without prescription, at least 10 (18%) should have been provided with a device, according to the most recent guidelines. In conclusion, notwithstanding intramuscular adrenaline being the first-line treatment of anaphylaxis, many episodes are still undertreated and the risk of anaphylaxis is still underestimated. More efforts should be made to promote the correct management of anaphylaxis among both healthcare-providers and patients.
LETTER TO THE EDITOR

IN VITRO ACTION OF SHO-SEIRYU-TO ON ALLERGEN-EXPOSED MONONUCLEAR CELLS

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Although Sho-seiryu-to (SST), used as a traditional herbal (Kampo) medicine mainly in China and Korea, is shown to have immunomodulating potential, such as an anti-allergic one, its underlying mechanism has not been completely clarified. To partially address the issue, we explored its effects on allergen-exposed mononuclear cells. Male balb/c mice were intraperitoneally administered ovalbumin (OVA: 20 µg) plus alum or vehicle twice (Day 0 and Day 14). At Day 21, mice were sacrificed and splenocytes (mononuclear cells) were isolated and cultured in the presence or absence of OVA with or without SST. Thereafter, helper T-related cytokines in the culture supernatants were evaluated by means of ELISA. Protein level of interferon-γ was lower than 5.0 pg/mL in the supernatants from OVA–non-exposed or -exposed mononuclear cells in the presence or absence of OVA stimulation. On the other hand, SST induced the cytokine from both types of mononuclear cells in the presence (P < 0.05) or absence of OVA stimulation as compared to corresponding control. By contrast, interleukin (IL)-4 level tended to be decreased by SST in OVA-non-exposed mononuclear cells as did IL-13 in both non-exposed and exposed mononuclear cells as compared to vehicle. In conclusion, immunoregulating efficacy by SST on allergy-prone subjects may include, at least in part, restoring helper T balance mainly through hyperproduction of IFN-γ against mononuclear cells such as lymphocytes.
It is widely accepted that inflammatory Bowel disease (IBD) arises from a dysregulated mucosal immune response to the enteric microbiota in the gut of a genetically susceptible individual. No definitive therapies are available for this inflammatory disorder. Therefore it became imperative to develop new strategies for treating this disease. Probiotics have emerged as a potential new therapeutic strategy for IBD, however their exact mechanisms of action is still poorly defined. In this study, we address the potential effect of a probiotic cocktail (Ultrabiotique®) composed of four live bacterial strains (L. acidophilus, L. plantarum, B. lactis and B. breve) to promote recovery from acute colitis. Probiotic was given to mice by oral gavage after the onset of colitis and the establishment of dextran sulfate sodium (DSS)-induced intestinal injury. Clinical parameters were monitored daily, histological scores of colitis and the production of nitric oxide (NO) and interferon-γ (IFN-γ) were determined. In addition, TLR4, NF-κB and iNOS colonic expression were examined. Probiotic treatment ameliorated clinical symptoms and histological scores. NO and IFN-γ production in plasma were decreased by probiotic. These results were associated with reduced TLR4, iNOS and NF-κB expression in colonic tissue. In conclusion, probiotic exerted anti-inflammatory effects and contributed to a rapid recovery of DSS-induced acute colitis.
LETTER TO THE EDITOR

MALIGNANT MELANOMA OF THE CONJUNCTIVA – SUCCESSFUL SURGICAL EXCISION OF THE PRIMARY TUMOR AND RECONSTRUCTION BY CONJUNCTIVAL AUTO TRANSPLANTATION FROM THE CONTRALATERAL EYE

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Malignant melanoma of the conjunctiva is a rare tumor with incidence of 0.5 cases/year per million population. It may also occur as de novo, as on the basis of preexisting melanocytic lesions (nevus or freckle) or most often from the so-called primary acquired melanosis of the conjunctiva (PAM). It metastasizes mainly lymphogenic and hematogenous. The size of the primary tumor lesion, histopathological findings and absolute tumor thickness are essential for unfavorable prognosis. Conjunctival auto transplantation from the other eye is modern and innovative, but also a seldomly feasible method of reconstruction after conjunctival excision of tumors in this area. We present a rare case of a 75-year-old patient with epithelioid cell malignant melanoma of the bulbar conjunctiva of the right eye, which de novo occurred, successfully treated by excision of the primary tumor and subsequent reconstruction by conjunctival auto transplant from the other eye. A very good therapeutic and aesthetic result was achieved.
ASSOCIATION OF THE IRF5 SNP rs2004640 WITH SYSTEMIC SCLEROSIS IN HAN CHINESE

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Systemic sclerosis (SSc) is a complex disease involving multiple genetic factors. An association of the IRF5 polymorphism with SSc was reported in Caucasian populations of Europe and North America, as well as in Japanese populations. The present study aimed to examine whether the SSc-associated SNP rs2004640 of IRF5 gene confer susceptibility to SSc and clinical features of SSc in a Han Chinese population. A Han Chinese cohort consisting of 424 SSc patients and 502 healthy controls were examined in the study. TaqMan assays were carried out to examine the SNP. Exact p-values were obtained (Fisher’s test) from 2x2 tables of allele counts and disease status. SSc patients of Han Chinese showed increased homozygous TT genotype of the rs2004640 (p = 0.027, odds ratio (OR) = 1.4, CI =1.03-1.93), which was significantly associated with pulmonary fibrosis of SSc and ATA-positive SSc of Han Chinese. The lcSSc and ACA-positive SSc of Han Chinese appeared also in association with the increased T allele frequency. However, the Chinese dcSSc did not show any association with the rs2004640. The results were consistent with previous reports in other ethnic populations in supporting the notion that polymorphisms of IRF5 may play an important role in susceptibility to SSc.
LETTER TO THE EDITOR

WRONG MELANOMA THICKNESS MEASUREMENT: CHECK IT OR LEAVE IT?

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Cutaneous malignant melanoma (CMM) is one of the most aggressive forms of skin cancer, accounting
for about 90% of deaths from cutaneous neoplasms, and its incidence has increased significantly in recent
years. According to the 2012 European criteria for diagnosis and treatment of malignant melanoma,
diagnosis should be based on the combination of clinical features, dermoscopic data and histological
examination, preferably after excisional biopsy. Tumour thickness and other parameters for local staging
according to the AJCC classification should be included in the pathology report. Although many factors
influence the prognosis and course of the disease, it has been established in a number of studies that tumour
thickness is the most important parameter. Therapy of malignant melanoma in its initial stages mostly
consists of wide local excision with 1 to 2 cm margins, and sentinel lymph node biopsy that is usually
performed in cases of tumours with a thickness greater than 1 mm. We present the case of a 58-year-
old Bulgarian male with cutaneous superficial spreading malignant melanoma, in which, after complete
excision, histological examination established an inaccurate tumour thickness (0.7 mm), with consequent
inadequate staging and further management. After reassessment of the results in another institution (as
well as their confirmation by two additional independent histopathology laboratories in our country –
1.92 mm), in the National Oncological Hospital where the patient was initially evaluated, sentinel lymph
node biopsy was not performed, contrary to the generally accepted European and World standards. With
the present case we raise some current issues regarding diagnosis and therapy of Bulgarian patients (not
only in the case presented) with malignant melanoma in the 21st century, and discuss the urgent need
for external quality control procedures and standardization of the histopathologic reporting, which is of
paramount importance in the staging and subsequent management of these patients.
A growing body of evidence presents a link between chronic inflammatory rheumatic diseases and atherosclerosis. To evaluate subclinical carotid atherosclerosis in an elderly group of patients with primary Sjögren syndrome compared with a control group matched for age, sex, ethnicity and cardiovascular risk factors, we enrolled 18 patients with Primary Sjögren Syndrome (mean age 65±5.93 SD) and 18 mild Osteoarthritic patients (mean age 66±5.94 SD) from the outpatient department of Rheumatology, University “Campus Bio-Medico, Rome, Italy, matched for age, sex, ethnicity and cardiovascular risk factors. A duplex Doppler sonographic study of carotids was performed in order to evaluate intima-media thickness (IMT), stiffness and haemodynamic parameters [resistivity and pulsatility indices (RI and PI, respectively)]. No significant difference was found between primary Sjögren syndrome and control patients in IMT, stiffness and haemodynamic parameters. The lack of significant difference in subclinical atherosclerosis between elderly primary Sjögren syndrome and control matched patients, indicates that traditional cardiovascular risk factors, immunologic alterations and chronic inflammation do not influence the progression of vascular damage in the carotid circulation of patients with median disease duration of 6.5 years.
LETTER TO THE EDITOR

BRADYKININ B2 RECEPTOR ANTAGONIST OFF LABEL USE IN SHORT-TERM PROPHYLAXIS IN HEREDITARY ANGIOEDEMA

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Hereditary angioedema type I (HAE-C1-INH) is an inherited disorder characterized by repeated severe angioedema attacks mostly triggered by traumas, emotional stress, increased estrogen levels or surgical procedures, in particular, odontostomatological interventions. Icatibant, a bradykinin B2 receptor antagonist, has been approved for treatment of HAE attacks. In this paper we describe the “off label” administration of icatibant as short-term prophylaxis of dental extraction in a patient with HAE with the aim of preventing perioperative angioedema attacks. The drug showed an effective and safe profile. Thus, a short-term prophylaxis of angioedema attacks in patients with HAE may be arranged on a multidisciplinary basis, according to the clinical history of each single patients.
The detection of *Aspergillus* antigen (galactomannan) is considered a reliable marker for the diagnosis of invasive aspergillosis (IA), yet the sensibility and specificity of the assays commonly employed in routine are not optimal. The aim of the present study was to investigate whether the detection of another panfungal antigen, the (1,3)-\(b\)-D-glucan could have an auxiliary role in the identification of patients with IA. The study was carried out on 63 sera belonging to patients who had been screened for galactomannan, according to the clinical suspect of IA. Our data show that the positive galactomannan results were not confirmed by positive (1,3)-\(b\)-D-glucan results in patients receiving therapy with beta-lactam antibiotics associated with tazobactam, whereas in all the other cases, with the exception of four, the results of the (1,3)-\(b\)-D-glucan test were confirmatory of the galactomannan results.
LETTER TO THE EDITOR

SEVERE SEPTAL PANNICULITIS IN A MULTIPLE SCLEROSIS PATIENT TREATED WITH INTERFERON-BETA

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We report a memorable case of severe septal panniculitis in an MS patient following the subcutaneous administration of interferon beta-1b, manifesting as a painful, indurated, erythematous lesion of the thigh, which appeared at the injection site.
LETTER TO THE EDITOR

EFFECT OF BETAMETHASONE IN COMBINATION WITH ANTIBIOTICS ON GRAM POSITIVE AND GRAM NEGATIVE BACTERIA

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Betamethasone is an anti-inflammatory steroid drug used in cases of anaphylactic and allergic reactions, of Alzheimer and Addison diseases and in soft tissue injuries. It modulates gene expression for anti-inflammatory activity suppressing the immune system response. This latter effect might decrease the effectiveness of immune system response against microbial infections. Corticosteroids, in fact, mask some symptoms of infection and during their use superimposed infections may occur. Thus, the use of glucocorticoids in patients with sepsis remains extremely controversial. In this study we analyzed the in vitro effect of a commercial formulation of betamethasone (Bentelan) on several Gram positive and Gram negative bacteria of clinical relevance. It was found to be an inhibitor of the growth of most of the strains examined. Also the effect of betamethasone in combination with some classes of antibiotics was evaluated. Antibiotic-steroid combination therapy is, in such cases, superior to antibiotic-alone treatment to impair bacterial growths. Such effect was essentially not at all observable on *Staphylococcus aureus* or Coagulase Negative *Staphylococci* (CoNS).
LETTER TO THE EDITOR

NASAL CYTOLOGICAL ASSESSMENT AFTER CRENOTHERAPY IN THE TREATMENT OF CHRONIC RHINOSINUSITIS IN THE ELDERLY

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Chronic rhinosinusitis (CRS) determines irreversible alterations of the nasal mucosa with consequent impairment of ciliary movements and, therefore, mucociliary clearance (MCC). People of all ages can be affected by CRS but the elderly are subjects at the highest risk. CRS in the elderly with an age-related physiological impairment of nasal respiratory function, often accompanied by other chronic diseases, requires additional therapies to be added to the numerous daily medications. Since the currently available therapies for CRS include the use of drugs that can have adverse effects and contraindications, crenotherapy could represent a therapeutic option. Indeed, because the adverse effects and contraindications of crenotherapy are scarce, it can be safely used in elderly patients with comorbidities. The aim of this study is to evaluate the nasal cytological assessment after crenotherapy in elderly subjects with CRS. Two groups, comprising a total of 84 elderly subjects with CRS, were treated with crenotherapy with sodium chloride sulphate hyperthermal water rich in mineral salts (group I, n=49) and saline solution (group II n=35). Cytological assessment for both groups took place at baseline (T0) and 1 month after treatment (T30). At T30 the nasal cytological assessment showed statistically significant improvements in the ciliary motility and in the count of neutrophils and spores in group I, but not in group II. Conversely, there were no significant differences in the count of eosinophils, mast cells, bacteria and biofilm in either group. Our data for the first time focused on the role of crenotherapy in the improvement of cytological assessment of CRS in the elderly.
LETTER TO THE EDITOR

EFFECTS OF GLUCOSAMINE AND NUCLEOTIDE ASSOCIATION ON FIBROBLAST:
EXTRACELLULAR MATRIX GENE EXPRESSION

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Glucosamine (Gluc) is a drug used as an anti-inflammatory in moderate forms of knee arthrosis. A further off label use of Gluc is in the anti-aging treatments associated with Polideoxiribonucleotide (PDRN) through intra-dermal injection for a procedure called bio-stimulation. An unexpected effect on cultured dermal fibroblasts, during an experimental study on the gene activation in aesthetic bio-stimulation, was observed. The results have potential application in orthopaedic medical therapy. Fibroblast primary cultures were carried out, seeding cells on a layer of Gluc or PDRN alone or in combination for 24 h. Real Time-PCR was performed to investigate several gene expressions. The MMP13 and the IGF-I gene expression in fibroblast cultures were strongly inhibited after 24 h of incubation with the association of Gluc and PDRN, whereas Gluc and PDRN alone produced a modest inhibition of IGF-I and an activation of MMP13. MMP13 is present in osteoarthritic cartilage and this enzyme plays a significant role in cartilage collagen degradation. IGF1 is involved in growth and development and is successfully used in tissue-engineering for cartilage repair. Based on the reported data, we infer that the association of Gluc and PDRN has a potential application in cartilage therapy. Additional basic science and clinical studies are needed to confirm this preliminary report.