Osteoarthritis (OA) requires long-term treatment, therefore, tolerability is a key factor in treatment choice. Hyaluronic acid (HA), a glycosaminoglycan with viscoelastic properties, a major component of synovial fluid and the extracellular matrix of the joint cartilage, plays key roles in synovial fluid viscosity and maintaining normal cartilage. Viscosupplementation is an intra-articular (IA) injection of exogenous HA in an effort to delay joint mobility loss. Commercially available viscosupplementation includes HA of different average molecular weight (MW), concentration and origins, with varying tolerability. This review describes the tolerability and safety profile of Sinovial® in knee and hip OA. A literature search of PubMed using the search queries [Sinovial® OR hyaluronic acid OR hyaluronan] and [intra-articular OR osteoarthritis] was performed using terms as medical subject headings and free text searches. Studies were selected manually for inclusion in this review. Sinovial® is a low-medium MW HA of non-avian origin, produced by biofermentation to ensure the product is pure and free of allergenic animal proteins. We analyzed data regarding the tolerability of Sinovial® in OA patients. This formulation has a favorable tolerability profile; no systemic reactions have been reported and most adverse events (AEs) are mild, transient and easily managed local injection site reactions. Reactions – pain and burning at the injection site – are typical of IA injections. AEs with Sinovial® used in the hip are similar to knee OA.
There is a certain consensus that some probiotics can significantly help in preventing and relieving the symptoms of gastrointestinal diseases and atopic diseases in general, but their use in respiratory tract infections has only been marginally investigated. The main aim of this review is to evaluate what is known about the impact of probiotics on pediatric respiratory tract infections in order to verify whether more data are needed before they can be used on infants and children with respiratory problems. Analysis of the literature shows that our knowledge is limited to the prevention of upper respiratory tract infections (URTIs). The very few studies carried out so far seem to indicate that probiotic administration may have some advantages in this regard, but the great limitation is that nothing is known about the susceptible micro-organisms or treatment regimens. Furthermore, URTIs are very limited clinical problems and it seems unreasonable to use a treatment whose efficacy and safety has not been completely clarified as means of preventing them. No data are available concerning the treatment of URTIs. There is a need for further research into the role of probiotics in treating respiratory infections and preventing more severe respiratory problems, including those involving the lower respiratory tract.
EDITORIAL

SKIN, INFLAMMATION AND SULFUROUS WATERS: WHAT IS KNOWN, WHAT IS BELIEVED

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One could argue that balneotherapy and mud therapy would have not lasted 2,000 years or so if they were not effective. No doubt a long history cannot be taken per se as scientific proof of efficacy. Some empiricism is still present in the field: the concept of spa itself is quite confounding, whereas spring waters are used for leisure purposes but also for non-acute patient therapy and late phases of clinical recovery. These confounding elements ultimately feed the opinion of those who aprioristically reject any potential beneficial effect of balneotherapy: instead, it should at least generate questions that deserve scientific answers. Clinical practices sequentially integrating pharmacological therapy with those natural principles for which a sufficient scientific demonstration is available, would probably cut the costs of public health, generating widespread advantages for the community. Recently, it has become evident that mineral waters may have intrinsic pharmacological properties. Of the numerous salts dissolved in thermal waters that might show pharmacological properties, for certain hydrogen sulfide (H₂S) contained in sulfurous waters is the one that has obtained greater scientific attention, to which should be added the extensive scientific effort recently dedicated to H₂S as a cellular gasotransmitter, independently from its natural sources. Dermatology and cosmetics are among the most studied applications of sulfurous waters, around which, however, some empiricism still confounds opinions: we therefore considered that a state-of-the-art focus on this topic might be timely and useful for future studies.
ORAL LICHEN PLANUS: NOVEL ACQUISITIONS IN THE PATHOGENESIS AND TREATMENT

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Lichen planus (LP) is a mucocutaneous disease of chronic inflammatory nature, commonly seen in dermatological and dental clinics; it is a relatively common disorder of stratified squamous epithelia, frequently exclusively involving the oral cavity. Oral Lichen Planus (OLP) is often asymptomatic, the atrophic-erosive form can cause symptoms ranging from burning sensation to severe pain, interfering with speaking, eating, and swallowing. Lichen planus is regarded as a premalignant lesion. This review discusses the role of hepatitis C virus (HCV), bacterial and fungal infection in LP. Analysing the seroprevalence of HCV infection in LP patients and patients with oral OLP in particular, which was the case in the vast majority of studies, the association varied from 0% to 62% and seemed to be connected to the high HCV seroprevalence in the general population. Candida albicans is present in about 37% of oral LP lesions. The aim of this review is to summarize what is new in the pathogenesis and treatment of OLP.
Mast cells in the tissue are located close to nerves in and around the small vessels where they orchestrate important immune response after antigen recognition through Toll-like receptors. Mast cells can activate T and B lymphocytes and dendritic cells and have been postulated to act directly within tissue allografts and/or to induce indirect effects via inflammatory mediator release, therefore they have been shown to play an indispensable role in allograft tolerance. Major limitation in the success of transplantation is the immune response of the recipient to the donor tissue. The failure of tissue grafting is caused by an inflammatory reaction called rejection. Mast cells play a role during immune response and are elicited with transplanted allograft and also may exhibit their immune-regulatory effects directly through secretion of modulatory cytokines and activation of metabolic pathways. However, the role of mast cells in transplantation is poorly understood. The most severe rejection episodes have been found in patients with an increased number of mast cells. Mast cell mediators which can activate latent forms of TGF-β or increase angiotensin II levels are capable of inducing fibrosis through various mechanisms, activating fibroblasts and inducing collagen synthesis. Mast cells are also implicated in regulatory T-cell functions and are required to sustain peripheral tolerance via Treg, therefore there is an interaction between mast cells and Treg cells. Treg create IL-9 in enhancing mast cell growth and chemotaxis, suggesting that Treg and mast cells form a functional unit that mediates graft tolerance. In this study we concentrate our attention on the role of mast cells in rejection of allografts and try to understand the role of mast cell-related immune mechanisms in organ transplantation.
INONOTUS OBLIQUUS SUPPRESSES PROLIFERATION OF COLORECTAL CANCER CELLS AND TUMOR GROWTH IN MICE MODELS BY DOWNREGULATION OF β-CATENIN/NF-κB-SIGNALING PATHWAYS


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Chaga mushroom (Inonotus obliquus) has been used as a folk remedy for several illnesses including gastrointestinal disorders. We recently reported the potent anti-inflammatory effect of chaga extract in experimental colitis. However, its effects on colorectal cancer (CRC) have not been clearly elucidated. We investigated the effects of an aqueous extract of Inonotus obliquus (IOAE) in vitro in HCT116 and DLD1 cell lines and in vivo for adenoma in APCMin/+ mice and colitis-associated colon cancer in AOM/DSS-treated mice. Results show that IOAE suppressed the proliferation of both cell lines, and inhibited the growth of intestinal polyps in APCMin/+ and colon tumors in AOM/DSS-treated mice. IOAE induced mitochondrial intrinsic pathway of apoptosis, autophagy, and S phase cell cycle arrest. IOAE suppressed the expression levels of iNOS and Cox-2 and mRNA levels of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α and IFN-γ) in the intestine of mice models. IOAE suppressed the nuclear levels of β-catenin and inhibited its downstream targets (cyclin D1 and c-Myc) along with CRC oncogene CDK8. IOAE inhibited the expression of NF-κB at cytoplasmic and nuclear levels. Our results demonstrate that IOAE possess potent anti-inflammatory and anti-proliferative properties through downregulation of Wnt/β-catenin and NF-κB pathways. Considering recent anticancer approaches involving natural products with minimal side effects, we advocate that Inonotus obliquus could be a beneficial supplement in prevention of colorectal cancer.
IMPACT OF AGE AND AUTOANTIBODY STATUS ON THE GENE EXPRESSION OF SCLERODERMA FIBROBLASTS IN RESPONSE TO SILICA STIMULATION

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Environmental factors are believed to play an important role in the pathogenesis of systemic sclerosis (SSc). Silica exposure has been implicated as potentially hazardous in epidemiological studies of SSc. It can activate fibroblasts to express profibrotic genes at certain conditions. The aim of this study is to examine whether the fibroblasts of SSc patients respond to silica particles with specific gene expressions differentially from normal control fibroblasts. The fibroblasts obtained from skin biopsies of 96 SSc patients and 104 controls were examined. Silica particles were used to perturb the cultures of the fibroblasts in time-course and dose-response assays. The transcript levels of COL1A2, COL3A1, MMP1, MMP3, TIMP3 and CTGF genes of the fibroblasts were measured with quantitative RT-PCR. The results showed that the expressions of all six genes in SSc fibroblasts under silica perturbation appeared significantly different from normal control fibroblasts. In age stratified analysis, compared to control fibroblasts, SSc fibroblasts from patients at age 30–40 years and 50–60 years displayed significantly decreased expressions of MMP1 gene in all dosage assays and increased expression of COL3A1 genes started at low dosages perturbation of silica particles, respectively. In autoantibody stratified analysis, specific gene expression patterns were significantly associated with autoantibody-subgroups of fibroblasts. A common feature of SSc fibroblasts was unstable and a wide range of gene expression changes in response to silica perturbation. Our studies may suggest an altered intrinsic dynamic control in SSc fibroblasts. In addition, sensitivity and specificity of SSc fibroblasts to potentially hazardous environmental trigger is age and autoantibody-subgroup-dependent. The fibroblasts of SSc patients at age 30–60 years may be more sensitive to silica perturbation toward a profibrotic gene expression.
A NOVEL INTERLEUKIN-10 DNA MUCOSAL DELIVERY SYSTEM ATTENUATES INTESTINAL INFLAMMATION IN A MOUSE MODEL

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Inflammatory bowel diseases (IBD) describe a group of complex intestinal disorders characterized by inflammation in the gastrointestinal tract. Current treatments for IBD include the use of anti-inflammatory drugs; furthermore, recombinant lactic acid bacteria have been used as a therapeutic vehicle for anti-inflammatory agents in IBD models. Interleukin-10 (IL-10) is one of the most important anti-inflammatory cytokines; however, its oral administration is limited because it is quickly degraded in the gastrointestinal tract and systemic treatments have led to undesirable side effects. In this study, an engineered invasive strain of Lactococcus (L.) lactis producing Fibronectin Binding Protein A (FnBPA+), from Staphylococcus aureus capable of delivering, directly inside eukaryotic cells, an eukaryotic DNA expression vector containing the ORF coding for IL-10 of Mus musculus (pValac:il-10) was developed and its functionality was evaluated using in vitro and in vivo assays. Functionality of the plasmid and the invasive strain was demonstrated by transfection and invasiveness assays using cell cultures and in vivo in mice by fluorescence microscopy. TNBS inoculated mice that received this novel strain showed lower damage scores in their large intestines (at both macroscopic and microscopic levels), lower microbial translocation to liver, and increased anti-inflammatory/pro-inflammatory cytokine ratios compared to mice that received L. lactis FnBPA+ without the pValac:il-10 plasmid. The effectiveness was demonstrated of this novel DNA delivery therapeutic strategy in the prevention of inflammation using a murine model of colitis.
The aim of the present investigation is to examine the changes in the number of somatostatin–like immunoreactive (SOM-LI) enteroendocrine cells in various parts of the canine gastrointestinal (GI) tract during canine inflammatory bowel disease (IBD). The distribution of SOM-LI enteroendocrine cells was studied using the double-labeling immunofluorescence technique with antisera against chromogranin A (CgA; used here as a marker of enteroendocrine cells) and somatostatin (SOM). Evaluation of the number of CgA-positive cells, which also contained SOM in the mucosal layer of canine stomach, duodenum, jejunum and descending colon was based on the counting of such cells per unit area (0.1 mm²). In physiological conditions, the number of SOM-LI enteroendocrine cells has been shown to constitute 5.30±2.07 in the stomach, 2.23±0.56 in the duodenum, 1.86±0.48 in the jejunum and 1.19±0.36 in the descending colon. Canine IBD caused an increase in the number of cells studied in the stomach (to 9.55±1.46) and the jejunum (to 3.84±1.16), while the changes observed in the duodenum and the descending colon have not been statistically significant. The obtained results suggest that SOM-LI enteroendocrine cells, as well as somatostatin, may be involved in pathological processes during canine IBD. Moreover, this study can be treated as the first step of application of SOM and/or its analogues in the treatment of canine IBD in the future.
Although several studies have shown physiological functions of interleukin (IL)-32, the role of IL-32 in liver has not yet been reported. This study was initiated to examine the effects of IL-32γ on APAP-induced acute hepatic failure in IL-32γ transgenic mice. IL-32γ overexpressing and non-transgenic mice received 500 mg/kg Acetoaminophen (APAP) intraperitoneally. Serum alanine transaminase and aspartate transaminase were significantly lower in the APAP treated IL-32γ overexpressing mice compared with those APAP-treated non-transgenic. IL-32γ markedly reduced a restricted area of the necrosis and inflammation. APAP-induced reduced glutathione depletion, induction of nitric oxide and lipid peroxidation, and cytochrome P4502E1 expression was significantly lowered in the IL-32γ overexpressing mice. Elevation of Kupffer cells and natural killer cells by APAP were reduced in the IL-32γ overexpressing mice. The expression of IL-1α, IL-1ra, macrophage inflammatory protein-2, C-C motif chemokine ligand 5 and tissue inhibitor of metalloproteinase-1 was increased by APAP in non-transgenic mice, and were lowered in the IL-32γ overexpressing mice. The expression of IL-1α, IL-1ra, macrophage inflammatory protein-2, C-C motif chemokine ligand 5 and tissue inhibitor of metalloproteinase-1 was increased by APAP in non-transgenic mice, and were lowered in the IL-32γ overexpressing mice. The results indicate that IL-32γ could effectively inhibit drug-induced hepatic failure, and reduce the number of cytotoxic immune cells and pro-inflammatory cytokine production through reduced activities of NF-κB and STAT1. This might be attributable to lowering APAP-induced liver toxicity in IL-32γ overexpressing mice.
EFFECTS OF 17ß-ESTRADIOL ON THE ACUTE NECROTIZING PANCREATITIS AFTER ONSET IN RATS*

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The aim of this study was to investigate the influence of 17ß-estradiol (E₂) on acute necrotizing pancreatitis (ANP) induced by glycodeoxycholic acid in rats. Rats were divided into six groups as sham + saline, sham + single dose E₂ (SDE₂), sham + multiple dose E₂ (MDE₂), ANP + saline, ANP + SDE₂, and ANP + MDE₂. ANP in rats was induced by glycodeoxycholic acid. The extent of acinar cell injury, mortality, systemic cardiorespiratory variables, functional capillary density (FCD), renal/hepatic functions, and changes in some enzyme markers for pancreatic and lung tissue were investigated during ANP in rats. The induction of ANP resulted in a significant increase in the mortality rate, pancreatic necrosis, and serum activity of amylase, alanine aminotransferase (ALT), interleukin (IL)-6, lactate dehydrogenase (LDH) in bronchoalveolar lavage (BAL) fluid, serum concentration of urea, and tissue activity of myeloperoxidase (MPO) and malondialdehyde (MDA) in the pancreas and lung, and a significant decrease in concentrations of calcium, blood pressure, urine output, pO₂, and functional capillary density (FCD). The use of E₂ did not alter these changes. E₂ demonstrated no effect on the course of ANP in rats. Therefore, it has no value in the treatment during acute pancreatitis.
THROMBOMODULIN GENE POLYMORPHISM (C1418T) IS ASSOCIATED WITH THE DEVELOPMENT OF CORONARY ALLOGRAFT VASCULOPATHY

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Thrombomodulin (TM) is the endothelial cell membrane-bound anticoagulant protein cofactor in the thrombin-mediated activation of protein C. Previous evidence has been reported regarding the association between TM polymorphisms and coronary artery disease. Allograft rejection-mediated vasculopathy is the main cause of death at more than one year after heart transplantation. However, whether TM polymorphism is associated with allograft rejection is still unclear. We analyzed the TM gene polymorphism C1418T using allele-specific primers in a PCR assay in 60 patients who underwent heart transplantation. The retrospective clinical data were collected and tested for any correlations with the TM gene polymorphism. We separated the patients into 2 groups according to their TM genotype (group 1: CC genotype; group 2: CT or TT genotype). Additionally, we generated expression constructs (TM full length-C1418 and TM full length-T1418) and performed in vitro studies to explore the correlation between the TM C1418T polymorphism and the migration of smooth muscle progenitor cells and monocytes, which may be involved in the development of vasculopathy. The results showed that the levels of CD68, C4d, PAS, and Masson staining in the CT/TT genotype group increased at year 1 and continued to increase throughout the 3 years. These levels were higher than those observed in the CC genotype group. The ISHLT-WF2004 grade of the CT/TT genotype group was significantly different from that of the CC genotype group at the same time point post-transplantation. The coronary allograft vasculopathy (CAV) score was significantly different between the CC and CT/TT genotype groups at 1 and 3 years post-transplantation. Our in vitro studies demonstrate that both smooth muscle progenitor cells and monocytic THP-1 cells with either the CT-1418 or the TT-1418 TM genotype have higher migratory abilities than cells with the CC-1418 genotype. Our results support a significant association between the TM C1418T polymorphism and the development of CAV after heart transplantation in the short- to medium-term.
Reumatoid arthritis (RA) is an autoimmune disease which has been studied experimentally using a wide variety of animal models including collagen-induced arthritis (CIA). Using this CIA model we studied the therapeutic effects and mechanism of action of Ebosin, a novel exopolysaccharide produced by \textit{Streptomyces} sp. 139, on arthritis. Ebosin at 200, 400 and 600 mg/kg/day was orally administered to rats respectively between day 10 and 30 after immunization with chicken type II collagen. With the treatment arthritic progression was remarkably suppressed. Levels of anti-type II collagen-specific antibody, IL-1β and TNF-α were significantly lower in the Ebosin-treated CIA rats compared with the untreated controls. In cultured fibroblast-like synoviocytes (FLS), remarkable suppression of IL-1β, TNF-α and IL-6 production was detected at both protein and mRNA levels after Ebosin administration. Ebosin also resulted in lower activities of IL-1β-converting enzyme and TNF-α-converting enzyme in FLS. Based on these results, it is concluded that development and progression of rat CIA can be significantly suppressed by orally-administrated Ebosin. The therapeutic effect may be attributed to its inhibition in the production of IL-1β, TNF-α and IL-6 in the CIA rats.
Mast cells play important roles in innate immunity through their activation via toll-like receptors (TLRs) but also contribute to neuroimmunological responses and inflammation through their activation by the neuropeptide substance P (SP) via G\(\alpha_{i/o}\) proteins. This study aims to compare the effects of the TLR2 agonists peptidoglycan (PGN) and tripalmitoyl-S-glycero-Cys-(Lys)\(_4\) (Pam3CSK4) on SP-induced human mast cell activation. The human mast cell line LAD2 was employed and mast cell activation was determined by assays of \(\beta\)-hexosaminidase, IL-8 and intracellular calcium. TLR2 agonists did not cause degranulation, but induced the release of IL-8. Pretreatment of PGN and Pam3CSK4 inhibited SP induced degranulation but only Pam3CSK4 blocked SP induced calcium mobilization. SP-induced IL-8 release was synergistically enhanced by PGN but abolished by Pam3CSK4. Studies with inhibitors of key enzymes implicated in mast cell signaling revealed that synergistic release of IL-8 induced by PGN and SP involved calcineurin, ERK, NF-\(\kappa\)B and PI3K signaling cascades whereas Pam3CSK4 inhibited SP induced mast cell activation by interfering with the interaction between SP and G\(\alpha_{i/o}\) proteins. These findings suggest that activation of human mast cells can be differentially modified by TLR2 agonists via distinct signaling pathways through facilitating formation of different TLR2 heterodimers with other TLRs.
We previously demonstrated in young mice that in comparison with animals raised in an impoverished environment (IE), animals from an enriched environment (EE) show more severe dengue disease, associated with an increased expansion of memory T target cells. Because active older adults show less functional decline in T-cell adaptive immunity, we hypothesized that aged mice from EE would show higher mortality and T-lymphocyte expansion than mice from IE. To test this hypothesis, we administered serial i.p. injections of anti-DENV2 hyperimmune serum, followed 24 h later by DENV3 (genotype III)-infected brain homogenate. Control mice received equal volumes of serum but received uninfected brain homogenate. The presence of virus or viral antigens was indirectly detected by real-time quantitative RT-PCR and immunohistochemistry. Compared to infected IE animals, EE mice, independent of age, showed higher mortality and more intense clinical signs. Compared to young mice, the higher mortality of aged mice was associated with a higher degree of T lymphocytic hyperplasia in the spleen and infiltration in kidneys, liver, and lungs, but less viral antigen immunolabeling. We propose that a higher expansion of T cells and serotype cross-reactive antibodies are associated with disease severity in aged mice.
Health care workers (HCWs) are at high risk of blood borne infections including Hepatitis B virus (HBV) infection. HBV vaccination is recommended for HCWs but post vaccination testing of immune response (anti-HBs) is not routinely performed. In our study information on immune response after the first immunization schedule of HCWs is not available. By reason of the questions regarding long lasting immunity, we decided to assess the anti-HBs of HCWs who wished to check immune response after different times of vaccination and also unvaccinated persons in St. Marina University Hospital, Varna, Bulgaria. After informed consent, 341 HCWs were investigated. They were divided into 3 groups according to their status: Group A had no history of vaccination against HBV, Group B had no complete vaccination schedule and Group C had complete vaccination data. Of Group C, 32 had been vaccinated more than 10 years previously, 111 – 10-5 years previously and 48 – < 5 years previously. Quantitative detection of antibody to HBsAg (anti-HBs) by commercial ELISA was carried out. A total, positive immune response was detected in 35.6% (group A), 66.2% (group B) and 80.1% (group C) of HCWs investigated. Of Group C positive immune response was detected in 68.7%, 81.1% and 85.4% respectively of the time of vaccination. Detectable anti-HB was found in HCWs without HBV immunization, probably after unknown exposure to HBV. The lack of information regarding immune response after the first immunization schedule makes the interpretation of no detectible anti-HBs level 5–10 years post-immunization difficult. For the HCWs with anti-HBs loss, counseling for booster vaccine dose and consequent testing is mandatory.
The recovery of functional gait is the main target for subjects who have suffered a stroke. The methods designed to improve balance and gait appear to be essential for skills and autonomy and to reduce the costs of assistance. The aim of our study was to evaluate the improvement of stroke victims in the chronic phase through the rehabilitation of gait, balance and posture using postural re-alignment with specific body weight support. The study includes 20 subjects with residual hemiparetic gait after stroke. Evaluation with international rating scales, gait analysis and stabilometric test was carried out at the beginning and after the 1st and the 3rd month of therapy; a follow-up control was made 3 months after the end of the rehabilitation program. All subjects underwent the rehabilitation protocol with Dynamic Antigravity Postural System 2 times a week for 3 months and were also treated with high efficiency focused acoustic waves (ViSS) to increase strength and muscular endurance (300Hz) or to reduce spastic hypertonia (200-120 Hz). The study shows a significant improvement in gait and balance with the persistence of results at the follow-up 3 months after the end of treatment. The subjects showed an increase in walking speed, greater stability and a consequent reduction of sedentary lifestyle with less risk of complications or recurrence. In conclusion this rehabilitation program is efficient for posture and walking quality.
Low testicular volume (TV) is associated with a decreased testicular function. Several studies explored the conventional sperm parameters and the endocrine function in patients with low TV. No other parameters have been examined. On the basis of these premises, the aim of this study was to evaluate a non-conventional seminal parameter: seminal lymphocyte characterisation in men with low TV compared with that of subjects with normal TV. A further comparison was made between fertile men and infertile patients with low or normal TV (78 patients). The testis was considered normal in size when it had a volume between 15 and 25 cm$^3$, low-normal with a volume between 10 and 12 cm$^3$ and hypotrophic when the volume was <10 cm$^3$. Statistically significant differences were observed in the following sperm parameters: percentage of immature germ elements, peroxidase-positive leukocyte concentration and CD45$^{\text{pos}}$ leukocytes (p<0.05). A correlation analysis showed the presence of a positive linear relationship between CD45$^{\text{pos}}$ leukocytes and the percentage of immature germ elements ($r=0.88; p<0.05$) and between CD45$^{\text{pos}}$ leukocytes and the percentage of spermatozoa with phosphatidylserine externalisation ($r=0.90; p<0.05$) as well as a negative linear relationship between the percentage of spermatozoa with normal morphology and the seminal CD45$^{\text{pos}}$ leukocyte concentration ($r=-0.75; p<0.05$). The results of this study showed that patients with low testicular volume (<10 cm$^3$) have a significantly increased CD45$^{\text{pos}}$ concentration that is associated with increased percentages of immature germ elements, spermatozoa with signs of early apoptosis, and spermatozoa with abnormal morphology.
INFLAMMATORY PROFILE OF NEUROTROPHINS, IL-6, IL1-β, TNF-α, VEGF, ICAM-1 AND TGF-β IN THE HUMAN WALDEYER’S RING

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The palatine tonsils, nasopharyngeal tonsil (adenoid) and lingual tonsil constitute the major part of Waldeyer’s ring, with the tubal tonsils and lateral pharyngeal bands as less prominent components. The lymphoid tissue of Waldeyer’s ring is located at the gateway of the respiratory and alimentary tract and belongs to the mucosa-associated lymphoid tissue (MALT). Mucosae-associated lymphoid tissues are richly innervated and the mucosae contain peptidergic nerve endings associated with different types of cells and macrophages. The lymphatic tissue is known to interact with the nervous system and several organs implicated in the host response to a wide range of stressors. This study focuses on the expression of some neurotrophins (NTs), their high- and low-affinity receptors in human adenoid tissues, lingual and palatine tonsils via immunohistochemical analysis, as well as on the expression of some inflammatory cytokines and other tissue growth factors. Light microscopy immunohistochemistry showed human samples to be generally positive for all the NTs investigated (NGF, BDNF, NT-3) and their receptors (TrKA, TrKB and TrKC) with some different expression levels. IL-6, IL1-b, TNF-a, VEGF, ICAM-1 and TGF-b were also investigated by immunohistochemistry. These results suggest the presence of a pattern of neurotrophic innervation in the human lymphatic tissues which may play a role in sustaining inflammatory conditions and in modulating a close interaction between the nervous system and the different immune cellular subtypes. Our data also corroborate previous studies, suggesting that neurotrophins and inflammatory cytokines may mediate functional signals in lymphoid aggregates. In this context, owing to their widespread expression in immune organs and immunocompetent cells, NTs and inflammatory cytokines are potential candidates for a prominent role in the regulation of immune and neuroimmune interactions.
Rotator cuff lesions are quite common and in some cases Hyaluronic Acid (HA) can play a role in pain relief and in restoring functions. The aim of the study was to point out the correct indications for HA injection therapy through a prospective study: firstly defining the safety and efficacy of HA in the different grades of cuff tears, then evaluating the maintenance at 90 days, as secondary endpoint. A prospective, open-label uncontrolled study was developed. One hundred patients diagnosed with different rotator cuff lesions were divided into 4 grade-related groups based on a modified Neer’s classification. A cycle of 3 US-guided injections of medium-low weight HA was performed through the anterolateral way, one every two weeks. Follow-up was at 0, 15, 30, 45 and 90 days. VAS, Oxford-Shoulder-Score (OSS) and Constant-Murley were used for evaluations. In grade I and II, at day 45, a significant reduction of VAS and increase of Constant-Murley and OSS resulted. In grade IV VAS slowly decreased in the first 45 days, while OSS and Constant did not improve significantly. In grade III patients had no benefit from a clinical and subjective point of view. At ninety days the beneficial effect was still maintained in grades I, II and IV. Overall, the treatment showed a high tolerability profile. In conclusion, patients affected by bursitis or partial cuff tears benefit from HA, while in cuff arthropathy HA might only delay surgery or represent a palliative. In complete tears HA was not effective in pain relief or functional recovery.
OXIDATIVE STRESS AND LOW-GRADE INFLAMMATORY STATUS AS CARDIOMETABOLIC RISK FACTORS IN ITALIAN OCCUPATIONAL OVERWEIGHT/OBESE SUBJECTS

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Obesity is associated with increased risk of cardiometabolic diseases. Adipocytokines (e.g. leptin), produced by the endocrine function of adipose tissue, can contribute to cardiometabolic risk in overweight and obese people. Oxidative stress, imbalance between oxidants and antioxidants, is considered a cardiovascular risk factor. High serum oxidized LDL (oxLDL) levels, marker of lipid peroxidation, a primary cause of atherosclerosis, can contribute to its progression. The aims of this study are to assess markers of oxidative status and cytokine profile and evaluate their role as cardiometabolic risk factors and possible correlations. In this cross-sectional study, we enrolled 76 occupational overweight-obese adults (46 females, 30 males; aged 46.8±9.5; BMI 33.7±4.8 kg/m²) without any previous cardiovascular disease. Oxidative status was measured by evaluating serum Reactive Oxygen Species (ROS) levels, Total Antioxidant Capacity (TAC) and oxLDL concentrations. All subjects’ soluble cytokine and adhesion molecule levels were evaluated by cytofluorimetric method and compared with 35 controls matched for sex and age. ROS and oxLDL levels were high in 84% and 92% of the study population, respectively, despite adequate TAC (68%). Female ROS levels were significantly higher than those of males (414±99.3 vs 318±48.2 UCarr, p<0.0001), while their oxLDL levels were lower (95.3±22 vs 105.2±19.4 U/L, p=0.1). Leptin and sICAM-1 (intracellular adhesion molecule involved in leukocyte migration to inflamed area) levels of the study population were significantly higher than those of controls (93.8±89.1 vs 25.3±23 ng/mL, p=0.0002 and 505.8±236.7 vs 339.2±119.6 ng/mL, p=0.0009, respectively). Overweight/obese occupational subjects showed oxidative stress conditions accompanied by low chronic inflammatory status, possibly contributing to increased cardiometabolic risk.
Bone resorption in edentulous regions often results in inadequate ridge for implant osseointegration. In order to overcome this problem, the use of osteoconductive biomaterials has been proposed as a carrier for different types of pharmacological molecules. Since raloxifene, a drug used in osteoporosis therapy, inhibits the osteoclast, but not osteoblast functions, it has been suggested to improve recovery during implant surgery. The present work evaluated in vitro the effect of raloxifene on two different cell populations: the human osteoblast-like cells (MG63) and osteoblasts derived from rat calvaria (MC3T3-E1). The morpho-functional investigations carried out showed a different behavior of the two cell lines. Raloxifene showed a stimulatory effect towards MG63 cell proliferation with a significant increase in cell viability after 7 days of culture. On the contrary, MC3T3-E1 cells showed a significant reduction in cell viability, when compared with the same cells at 72 h, or with the control cell population. The predominantly proliferative effect of raloxifene on MG63 cells is partly confirmed by the reduction of alkaline phosphatase activity, an early marker of osteoblast differentiation. The different effect of raloxifene on osteoblastic population in relationship to the type and age of the cell is an issue that needs further investigation.
The involvement of the oral cavity is rare but possible in patients with psoriasis. Most frequently different clinical entities are reported such as geographic tongue, fissures, angular cheilitis and ectopic geographic tongue. This interdisciplinary study was conducted by dermatologists in collaboration with dental hygienists on 22 patients with psoriasis. We examined 11 men and 11 women aged between 25 and 72 years during a period of 6 months. The involvement of the oral cavity was examined and a full photographic evaluation was carried out. A new assessment evaluation named Oral Psoriasis Area and Severity Index (OPASI) is proposed herein. The results obtained show the presence of oral lesions in 45.6% of the cases. This high involvement could be explained by the interdisciplinary nature of the study. We believe OPASI can be useful to assess the severity of lesions of the oral cavity, and may help to evaluate the response to therapy in relation to the Psoriasis Area and Severity Index (PASI) improvement.
The aim of this study was to analyze by Real-Time Polymerase Chain Reaction (PCR) possible differences in periimplant microbiota of patients without significant systemic diseases versus patients affected by non-insulin-dependent diabetes mellitus (NIDDM), both treated with dental implants with the same implant-abutment system. Patients suffering from NIDDM, and those with no history of major systemic diseases, treated with dental implants at the Prosthodontics Operative Unit of “Sapienza” University of Rome in the period February 2009 - March 2010 were considered. Clinical parameters as well as microbiological profile were evaluated for each implant site at 3, 6, 12, and 24 month follow-up. Crevicular fluid was collected for microbial sampling and analyzed by Real-Time PCR in order to identify the possible presence of Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum and Prevotella intermedia. Eight patients suffering from NIDDM and 22 with no history of major systemic diseases were included in the present investigation, each having received one to three dental implants. All the implants had been loaded 3 months after surgery, and the average follow-up after implant placement was 26.37±3.86. Clinical parameters showed no noticeable difference between the two groups, except for the Implant Stability Quotient (ISQ) that showed significantly lower values in NIDDM patients. A slightly higher amount of the considered pathogenic bacteria were retrieved in samples collected from patients with NIDDM (7.38x105) in comparison with those of healthy subjects (6.78x105), though the differences were below statistical significance. Within the limitations of the present study, a slight correlation was empirically detected between gene expression profiles of microbial populations and history of NIDDM, which however remained below the statistical significance. Further well-designed clinical studies may be useful to conclusively clarify the impact of subgingival microflora on the increased susceptibility of diabetic patients to periimplantitis.
UNDERESTIMATION OF ATYPICAL LOBULAR HYPERPLASIA AND LOBULAR CARCINOMA IN SITU AT STEREOTAXIC 11-GAUGE VACUUM-ASSISTED BREAST BIOPSY

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The aims of this study are to determine the frequency of diagnosis of atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) at stereotaxic-guided 11-gauge vacuum-assisted breast biopsy (VABB) and to assess the rate of underestimation of these at subsequent surgical excision and follow-up. Moreover, we aimed to define clinical, radiological and histological features of nonpalpable lesions in core biopsies that predict the lesion upgrade. Retrospective review of 11-gauge VABB was performed to identify the underestimation rate of nonpalpable lesions diagnosed as ALH or LCIS at VABB. Thirteen cases of ALH and 36 cases of LCIS were sent to surgery, 29 cases of ALH and 14 cases of LCIS were sent to follow-up. The clinical, mammographic and histologic features were assessed. The correlation between mammographic BI-RADS score and histological B-classification for both ALH and LCIS lesions were performed by Pearson’s test. Of 1,765 patients enrolled, lobular lesions (ALH and/or LCIS) occurred in 82 cases, and underestimation arose in 9 (10.9%). Two cases of underestimated ALH were upgraded to invasive lobular carcinoma and one to invasive ductal carcinoma. One case of underestimated LCIS was upgraded to ductal carcinoma in situ, two to invasive ductal carcinoma and three to invasive lobular carcinoma. The histology of the core and surgical specimens were compared. A significant difference was seen in the BI-RADS score (4-5 in 91% of underestimated lesions), and the size of the lesions (≥ 1.5 cm) for underestimated cases versus accurately diagnosed cases (p<0.001). Further significant parameters predictive for malignancy were the incomplete lesion removal by VABB and the presence of associated different breast lesions in the specimen. In conclusion, as far as ALH is concerned, we propose surgery as first choice when at least one of the following condition is respected: positive history for breast carcinoma, lesion >1.5cm, co-presence of high-risk lesions in the sample, signs of ductal involvement, high histological grading for atypia and follow-up in the other cases. Surgery is recommended in all cases of LCIS:
In vertebrate species, the MDM2 and MDM4 gene paralogs negatively regulate the activity of p53 family members and are involved in the development of a number of tumor types. Comparative genomic analyses have shown the presence of a single mdm homolog gene in invertebrates; its interaction with p53 and its involvement in tumor pathogenesis was demonstrated only in the mussel Mytilus trossulus. In addition to p53-related activity, a pro-inflammatory role for MDM2 in mammals has recently been described. In the present paper, we report the Real-time RT-PCR expression analysis of the mdm homolog gene in digestive gland tissue of Mytilus galloprovincialis collected from four different sites in the Campania region (Italy) during a single year. Our results revealed a positive correlation between the expression level of the mdm homolog and the percentage of chronic inflammatory lesions, both of which are increased during the summer period, suggesting a previously unidentified involvement of mdm in inflammatory processes in invertebrate species. Results obtained pointed out the potential interest of the use of mdm gene expression in marine food and seawater quality evaluation monitoring programs.

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Intra-articular injections of hyaluronic acid are a valid treatment option for patients with osteoarthritis. Differences in purity, origin, and molecular weight may influence the efficacy and safety of hyaluronic acid products, therefore, we evaluated the safety, efficacy, and duration of improvements following a single intra-articular injection of a low-medium molecular weight hyaluronic acid product of bacterial synthesis, Sinovial® One, on patients with osteoarthritis of the knee. The double-blind study enrolled 21 patients (24 knees) with symptomatic knee osteoarthritis, classified into moderate, severe and very severe osteoarthritis using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain functional Index and the Kellgren and Lawrence scales. At four months there was improvement in measured clinical parameters in 77.6% of the 24 treated knees, particularly in patients with moderate and severe osteoarthritis (improvement in 100% and 66.7%, respectively). No local or systemic adverse events were observed. These preliminary findings suggest that Sinovial® One is safe and effective for patients with knee osteoarthritis, providing long-lasting improvement in clinical parameters.
This study was conducted to compare the anti-inflammatory efficacy of nanoencapsulated and free-form diclofenac in rat. Diclofenac-loaded liposomes were prepared using the proliposome method. The anti-inflammatory effects of nanoencapsulated and free diclofenac were evaluated using the carrageenan-induced paw edema, formalin-induced paw licking and cotton-pellet-induced granuloma tests in vivo. For carrageenan-induced paw edema, 2 and 20 mg/kg liposome-encapsulated diclofenac showed significant paw volume reduction compared to free form diclofenac of equivalent dosage groups. In the formalin test, significant reduction in paw-licking time was observed in late phase for both liposome-encapsulated and free-form diclofenac (2 and 20 mg/kg) with the percentage of inhibition of 28.62, 60.17% for free-form diclofenac and 31.45, 78.84% for liposome-encapsulated diclofenac, respectively. In cotton-pellet-induced granuloma test 20 mg/kg free-form diclofenac showed significant reduction in the size of granuloma in both transudative and granuloma weight with percentage of inhibition of 42.93 and 49.26%, respectively, when compared to controls. Interestingly, 20 mg/kg nanoencapsulated diclofenac showed a larger reduction of the parameter with percentage of inhibition of 48.43 and 63.55%, respectively. Collectively, these results indicated that nanoencapsulated diclofenac exhibited statistically higher efficacy than free-form diclofenac when orally administered. Hence, clinical dosage may be reduced thereby reducing the drug’s adverse effects.
HASHIMOTO’S THYROIDITIS AND ENTERO-CHROMAFFIN-LIKE CELL HYPERPLASIA: EARLY DETECTION AND SOMATOSTATIN ANALOGUE TREATMENT

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Type IIIb polyglandular autoimmune disease comprises autoimmune thyroid disease (HT) and chronic atrophic gastritis (AIG). Hypergastrinemia, secondary to AIG, predisposes to gastric enterochromaffin-like cell (ECL) hyperplasia, a preneoplastic condition. We evaluated the prevalence of AIG, hypergastrinemia and ECL hyperplasia in HT patients. A secondary end-point was to assess the efficacy of treatment with a somatostatin analogue in HT patient with ECL hyperplasia. From 2009 to 2011, 146 HT patients were enrolled in a prospective study. All cases underwent hormonal profile, and parietal cell antibody (PCA), gastrin, and chromogranin A (CgA) serum level assays. Selected patients with elevated gastrin and CgA levels underwent gastro esophageal endoscopy (EGDS). Patients positive for ECL hyperplasia received Octreotide LAR 30 mg/28 days for 12 months. Gastrin and CgA assays were repeated every three months and EGDS after one year. The results show that gastrin and CgA were significantly higher than normal in 17/115 (14.7%) patients. Seven more HT had isolated PCA positivity and in the 17 PCA positive patients histology diagnosed AIG, corpus prevalent, with mild to moderate atrophy. Diffuse ECL hyperplasia of the gastric body was present in three subjects, one of them presenting a type-1 carcinoid. Gastrin and CgA levels were significantly reduced (p<0.01) after 3 months of therapy with a somatostatin analogue and returned to normal after 1 year. ECL hyperplasia regressed in all three patients. We suggest that selected HT patients may need a more accurate surveillance for early signs of gastric EC risk. In the case of altered values of gastrin and in the presence of PCA positivity, EGDS and histology should be performed for an early diagnosis of AIG and treatment of ECL hyperplasia.
A 34-year-old female was referred to us for a consultation of her dermatological lesions (pigmented lesions present in her oral cavity and on her right shoulder) in May 2007. These lesions had been present since childhood. Recently, the patient had developed seizures and a headache. An MRI of the brain showed the presence of two intracranial masses. The intracranial tumours were surgically removed whereas skin and mucosal lesions were biopsied. Histological findings of brain tumours were consistent with a diagnosis of “melanocytoma” while cutaneous lesions presented “benign dermal melanocytic infiltrations”. Whole brain irradiation was performed. After 3 months a new melanocytic skin lesion appeared on the scalp with histological picture similar to the other cutaneous ones. At the 5-year follow-up examination no recurrence of intracranial tumour or other skin or mucosal lesions were registered. According to the clinical and histological findings, we classify our case as a form of neurocutaneous melanosis in a young adult patient and we present it for the rarity of this syndrome, for the difficulty of the diagnosis, for the potential aggressive behaviour of intracranial lesions that necessitates a constant attentive follow-up and for the unusual feature of new developing skin lesion during the course of the disease.
LETTER TO THE EDITOR

THERMAL ABLATION OF EXTENDED LIVER CANCERS: ASSESSMENT OF TWO NEW BIPOLAR NEEDLE ELECTRODES

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In the United States, approximately 155,000 new cases of cancer of the liver and bile duct occur annually. Surgical resection of these tumors is considered the only treatment modality with a curative effect, but only 10% to 15% of patients with liver tumors are considered candidates for surgical resection. For this reason, several alternative treatment modalities have been developed. Radiofrequency energy has been the focus of increasing research and practice over the past few years. Recently, needle electrodes that encompass larger tissue volumes and radiofrequency generators that provide the increased power levels needed to heat these larger tissue volumes have become available. For this pilot study, we were interested in the evaluation of the capacity of larger sized needle electrodes to induce a predictable zone of tissue necrosis within diseased human liver. Furthermore, we wanted to prove safety and effectiveness of radiofrequency ablation in large sized liver tumors. In summary, the use of a bipolar 6 or 8 array electrode and power up to 180-220 watts energy was shown to produce controlled coagulation necrosis of targeted liver parenchyma and tumor with no observed complications.
LETTER TO THE EDITOR

ORTHOPEDIC THERAPY AND ALLERGIC CONTACT DERMATITIS: AN UNUSUAL CASE OF DOUBLE SENSITIZATION

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We report the first case of a double sensitization for two apparently non-related allergens: disperse red textile dye and topical ketoprofen. A possible explanation was that the topical gel medication could act as a vehicle between the skin and the textile red dye, underlining the importance of a “carrier-substance” to facilitate the allergen penetration and a possible sensitization to it.
Pulmonary function tests play an important role in the diagnosis and management of respiratory diseases in children. The purpose of the study was to evaluate lung function using the interrupter resistance technique (Rint) and spirometry (flow-volume and volume-time) in preschool children and to correlate the findings with respiratory symptoms. We studied 103 children (65 males, 38 females; mean age 5.2±0.7 years; range 3.6–5.8). For each child we collected family history concerning: respiratory diseases, skin prick tests, smoking during maternal pregnancy, history of gestational and neonatal period. All children performed lung function tests (Rint and spirometry) and skin prick test for inhalant and food allergens. Twenty-eight subjects (27.2%) had respiratory symptoms (RS). Expiratory Rint were performed in all subjects and spirometry was carried out on 76 children (73.8%). Spirometric indices were not statistically different between subjects without respiratory symptoms (controls) and RS children except for FEF$_{25-75}$ expressed as a percentage of the predicted value (RS: 81.5±13.7% vs controls: 94.5±15.8%; p < 0.001). Rint mean values were significantly higher in RS children than in controls (RS: 135.6±24.8% vs controls: 102.4±21.7%; p<0.0001). We found a statistically negative correlation between Rint and the following spirometric indices: FEV$_{0.5}$ (R= -0.696; p < 0.0001), FEV$_{1}$ (R=-0.728; p < 0.0001) and FEF$_{25-75}$ (R= -0.681; p <0.0001). In preschool children with respiratory disease we found significantly higher mean values of Rint and lower FEF$_{25-75}$ than in the control group and a significant negative relationship between Rint and spirometric indices.
LETTER TO THE EDITOR

ABNORMAL F-18 FLUORODEOXYGLUCOSE UPTAKE OF THE LUNG IN IMMUNOCOMPROMISED LYMPHOMA PATIENTS IN COMPLETE REMISSION: REPORT OF TWO CASES AND REVISION OF LITERATURE

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Limited data suggest that F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) may have a role in diagnosing infection. Here we present two cases of lymphoma patients in complete response (CR) who presented during follow-up dry cough and fever. Physical examination and serum evaluations were negative for lymphoma while whole body FDG-PET showed lung uptake which posed a differential diagnosis between relapse of lymphoma and an atypical pneumonia due to persistent lymphopenia. In both cases, cytology examination of sputum suggested Pneumocystis Jiroveci pneumonia (PJP). After appropriate antibiotic treatment, the follow-up examination showed complete resolution of the lung changes revealed by FDG-PET. False-positive results on FDG-PET were supposed to be due to the high uptake of FDG in non-neoplastic inflammatory cellular elements such as macrophages and lymphocytes. Our findings suggest that in cases of FDG-PET positive images in immunocompromised patients with previous hematologic disease, caution must be used, and differential diagnosis might include infections such as PJP in addition to relapse of disease.
LETTER TO THE EDITOR

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW: A RETROSPECTIVE STUDY ON THE ROLE OF DENTAL PROPHYLAXIS

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Clinicians use bisphosphonates in neoplastic and metabolic bone diseases. Osteonecrosis is the main complication of the maxillary bones, along with late mucosal healing with necrotic bone exposure, pain, burning sensation, paresthesia, and is commonly associated with osteonecrosis. In the dental unit of our department, we checked 181 patients, and divided them into three groups: patients who had not undergone therapy, patients who were currently undergoing bisphosphonate therapy, and those who had completed bisphosphonate therapy (but who had not been followed-up). For clinical management, patients were treated with a dental prophylaxis protocol or drug therapy, involving topical and/or systemic administration, and then underwent surgical resections when the osteonecrosis did not improve with any treatment. Variability with the percent of complications was statistically significant in the three groups. Despite the limited number of patients in this study, which will require further investigation, our experience demonstrated that preventive strategies in relation to complications are crucial. At this point, a satisfactory treatment for this pathology does not exist.
LETTER TO THE EDITOR

A CASE OF PERICARDITIS DUE TO ROSEOMONAS GILARDII IN A PATIENT WITH ANGIOSARCOMA OF THE PERICARDIUM

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Roseomonas gilardii is a Gram-negative slow growing coccobacillus that has been recognized as an opportunistic pathogen which can lead to infections, especially in immunocompromised and chronically ill patients. The organism is generally susceptible to carbapenems and aminoglycosides, but resistant to most of the cephalosporins. We report what we believe is the first case of a 72-year-old oncologic woman who developed a pericarditis caused by R. gilardii in Italy.
LETTER TO THE EDITOR

IN-VITRO ANALYSIS OF ANTIFUNGAL ACTIVITY OF EPIGALLOCATECHIN-GALLATE: PRELIMINARY STUDY

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Oral candisosis is an heterogeneous group of diseases, caused by different species of Candida fungus. The incidence of drug-resistant species is increasing dramatically; furthermore, in recent years higher incidences of non-albicans and antymycotic-resistant species of Candida have been reported, thus increasing necessity of a non-antibiotic agent, which should be both highly effective and safe. It has been showed that the main polyphenolic component of green tea, epigallocatechin-gallate (EGCG), has antibacterial activity; recently, it has been reported its antifungal activity too. We tested the effectiveness of a 0.20% EGCG (TEAVIGO ®) gel, a non-pharmaceutical product suitable for oral in vivo use, on four species of Candida yeast (C.albicans, C.parapsilosis, C.tropicalis, C.glabrata), evaluating its antifungal activity and its capacity to inhibit biofilm formation. The EGCG gel showed a remarkable activity against C. parapsilosis and C. tropicalis. This preliminary study confirms EGCG effectiveness on fungi; for this reason, a product with such a low concentration of EGCG could be used with no side-effect for every-day oral hygiene. Anyway, mechanisms of antifungal activity of EGCG are not comprehended and need further studies to better understand the reasons of some Candida species’ resistance.