NATALIZUMAB TREATMENT IN MULTIPLE SCLEROSIS PATIENTS: A MULTICENTER EXPERIENCE IN CLINICAL PRACTICE IN ITALY

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In this study, we review our current knowledge of the autoimmune etiopathogenesis of chronic rhinosinusitis with nasal polyps including bacterial infections, viral infections and immunomediated mechanisms and to discuss pathogenesis with relevance for pharmacotherapy. Relevant publications on the etiopathogenesis and treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) from 1977 to 2013 were analyzed. The characteristic signs and symptoms include appearance of relapsing nasal polyps, with typical symptoms such as nasal obstruction, nasal discharge and, usually, loss of the sense of smell. The etiology and pathogenesis remain unknown. Proposed theories of causation include bacterial or viral infections and immunomediated mechanisms. The autoimmune aetiology of of unknown origin or failure to respond to classic pharmacological treatments with nasal and oral steroids is now suspected. At present, the nature of the antigen trigger, the exact role played by B/T cells and anti-dsDNA autoantibodies in the pathogenesis of nasal polyposis remains unclear. Corticosteroids and surgery are the first line of treatment in CRSwNP. In the case of corticosteroid treatment failure, other drugs can be used such as rituximab, belimumab or omalizumab which have demonstrated clinical efficacy in the treatment of nasal polyposis with comorbid asthma. Immunosuppressive drugs such as methotrexate, and cyclophosphamide have also been used with varying degrees of success.
EDITORIAL

CORTICOTROPIN-RELEASING HORMONE, MICROGLIA AND MENTAL DISORDERS

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Microglia derive from mononuclear myeloid progenitors and are a major glial complement of the central nervous system. When microglia are activated they secrete inflammatory cytokines and toxic mediators which amplify the inflammatory response. In addition, the microglia inflammatory products are implicated in the neuronal destruction usually observed in various neurodegenerative diseases. Microglia cells express corticotropin releasing hormone (CRH) receptors, and activation of microglia by CRH releases bioactive molecules which have a biological effect in the brain and regulate several neurological diseases. CRH plays a pivotal role in stress responses and is a key mediator of the hypothalamic-pituitary-adrenocortical system. CRH is expressed in human mast cells, leading to autocrine effects and participates in inflammatory response together with neuropeptides, and stimulates mast cells. IL-33-activated mast cells release vascular endothelial growth factor in response to CRH and act synergistically to increase vascular permeability. CRH also up-regulates IL-18 expression by increasing intracellular reactive oxygen in microglia cells. Here we report the relationship between CRH, microglia and mental disorders.
Thioredoxins (Trx) and glutaredoxins (Grx) are thiol oxidoreductases that are ubiquitously expressed, and are involved in several biological processes. The expression of thioredoxins and glutaredoxins is induced in many neoplasms, and correlates with prognosis in gallbladder and colorectal carcinoma. The aim of the present study was to examine the expression pattern of these proteins (redoxins) in hepatocellular carcinoma (HCC) and to correlate their levels with clinical features. Paraffin-embedded tissues from 25 patients resected for HCC and 15 patients resected for colorectal carcinoma (CRC) liver metastases were analyzed with immunohistochemistry. Our results showed that Trx1, Trx2 and Grx5 were upregulated in HCCs as compared to the respective surrounding liver. In comparison, almost all redoxins were upregulated in CRC liver metastases, with Trx1 and Grx3 being significantly more increased in the CRC liver metastases than in the primary HCC tumors. In HCC, Trx1 correlated significantly with cell proliferation, and with a trend towards increased levels with micro-vascular invasion, while expression of Trx2 decreased with tumor size. Trx1 levels were lower in tumors of males, smokers, and patients with high alcohol consumption. Grx2 levels were significantly higher in patients with metabolic syndrome. In conclusion, this study illustrates specific correlations of individual redoxins to clinical features of HCC, and implicates the redoxins in the pathogenesis of HCC.
Sarcoidosis is a granulomatous disease with an increased accumulation of T cells in lungs as a result of on-site proliferation and chemotaxis induced by chemokines. It has already been demonstrated that CCL3-5 levels were increased in BAL fluid of sarcoidosis patients. To analyze the expression of CCL3-5 chemokines by T-cell subtypes (CD4+, CD8+, Th1, Th2, Tc1 or Tc2) in the lungs of sarcoidosis patients, fifteen untreated sarcoidosis patients and eighteen control subjects were enrolled in this study. CD4+ and CD8+ cells were isolated from BAL fluid by positive magnetic selection. The expression of CCL3-5 and other cytokines in CD4+ and CD8+ cells were measured by flow cytometry. The percentage of CD4+ or CD8+ cells expressing CCL4 were significantly higher in sarcoidosis patients (22.3% and 58.1%) compared to those seen in healthy subjects (11.1% and 16.5%, \(P = 0.04\) and \(P = 0.02\), respectively). In addition, the expression of CCL3, CCL4 and CCL5 was significantly elevated in CD8+ cells (8.9%, 58.1% and 2.1%) compared to CD4+ cells (2.1%, 22.3% and 0.7%; \(P = 0.04\), \(P = 0.009\) and \(P = 0.04\), respectively), whereas CCL4 was expressed by significantly more Tc1 than Th1 cells in sarcoidosis patients (\(P = 0.006\)). Our study shows the possible role of CD8+ cells and CD4+ cells in recruiting T cells to the site of inflammation in sarcoidosis through the release of CCL4, either alone or together with Th1/Tc1-associated cytokines.
Multifactorial factors have been involved in atherosclerosis. An association has been shown between osteoporosis and carotid atherosclerosis. This work evaluates the effect of vitamin D on regression of atherosclerosis. Forty-eight male rabbits were divided into: Group Ia: [Standard diet + saline for 4 weeks]; Group Ib: [Standard diet + a high dose of vitamin D3 daily for 4 weeks]; Group IIa: [Cholesterol–enriched diet for 4 weeks]; Group IIb: [Cholesterol–enriched diet + a single high dose of vit D3, daily for 4 weeks. At the end of 4 weeks, the rabbits were sacrificed for assay in serum lipid profile, C reactive protein (CRP), vitamin D3 metabolite, calcium, soluble adhesion molecules (sVCAM and sICAM) and nitrite (NO) and malondialdehyde (MDA) released from isolated aortic rings. Results showed that vitamin D produced a significant reduction in the sera of lipid profile, CRP, and adhesion molecules, associated with a non-significant change in serum calcium and a significant increase in the body level of vitamin D3. Addition of vitamin D to the incubated aortic rings of the atherosclerotic rabbits resulted in a significant increase in NO and decrease in MDA release. It could be concluded that vitamin D has anti-atherosclerotic effects, and may exert these effects by inhibiting lipid peroxidation and stimulation of nitric oxide, resulting in attenuation of the inflammatory atherosclerotic process.
Unsweetened natural cocoa powder is enriched with nutraceutical abundance of anti-asthmatic compounds theobromine and theophylline. Cocoa powder, which is prepared after removal of the cocoa butter, contains about 1.9% theobromine and 0.21% caffeine. Anecdotal reports indicate that regular consumption of unsweetened natural cocoa powder (UNCP), a common practice in Ghana, West Africa, has the potential to reduce the tendency of asthmatic episodes. In the present paper we studied the effect of regular ingestion of aqueous extract of UNCP on hematological and histopathological changes that occur in ovalbumin (OVA)-sensitized guinea pigs. OVA-sensitized guinea pigs were challenged with aerosolized OVA 1 hour after ingestion of 300 mg/kg (low dose) or 600 mg/kg (high dose) of UNCP for 35 consecutive days. Histopathological and haematological changes in the OVA-sensitized guinea pigs were evaluated. Both negative and positive controls with distilled water and prednisolone, respectively, were used. OVA-sensitized guinea pigs demonstrated concentration-independent reduction in immune response to aerosolized OVA. There were no histo-architectural changes in the bronchiolar smooth muscles of the treated groups. Unsweetened natural cocoa powder has potential anti-asthmatic properties when administered orally at the doses tested.
Increasing evidence indicates that tumor microenvironment (TME) is crucial in tumor survival and metastases. Inflammatory cells accumulate around tumors and strangely appear to be permissive to their growth. One key stroma cell is the mast cell (MC), which can secrete numerous pro- and anti-tumor molecules. We investigated the presence and degranulation state of MC in pancreatic ductal adenocarcinoma (PDAC) as compared to acute pancreatitis (AP). Three different detection methods: (a) toluidine blue staining, as well as immunohistochemistry for (b) tryptase and (c) c-kit, were utilized to assess the number and extent of degranulation of MC in PDAC tissue (n=7), uninvolved pancreatic tissue derived from tumor-free margins (n=7) and tissue form AP (n=4). The number of MC detected with all three methods was significantly increased in PDAC, as compared to normal pancreatic tissue deriving from tumor-free margins (p<0.05). The highest number of MC was identified by c-kit, 22.2±7.5 per high power field (HPF) in PDAC vs 9.7±5.1 per HPF in normal tissue. Contrary to MC in AP, where most of the detected MC were found degranulated, MC in PDAC appeared intact. In conclusion, MC are increased in number, but not degranulated in PDAC, suggesting that they may contribute to cancer growth by permitting selective release of pro-tumorogenic molecules.
PRE-CLINICAL EVALUATION OF A NEW CORAL-BASED BONE SCAFFOLD


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Coral is used worldwide for bone reconstruction. The favorable characteristics that make this material desirable for implantation are (i) osteoinduction, (ii) and osteoconduction. These proprieties have been demonstrated by in vivo studies with animal models and clinical trials over a twenty-year period. Also poly(2-hydroxyethylmethacrylate) [poly(HEMA)] is a widely used biomaterial. By using coral and poly(HEMA), a scaffold for bone reconstruction application has been recently synthesized. Cytological, histological and genetic analyses were performed to characterize this new alloplastic material. Four samples were analyzed: (a) white coral (WC), (b) red coral (RC), (c) WC plus polymer (WCP) and (d) RC plus polymer (RCP). Quantification of mitochondrial dehydrogenase activity by MTT assay was performed as indirect detector of cytotoxicity. In vivo effects were revealed by implanting corals and coral-based polymers in rabbit tibia. Samples were collected after 4 weeks and subjected to histological analysis. To evaluate the genetic response of cells to corals and coral-derived polymers an osteoblast-like cell line (i.e. MG63) was cultured in wells containing (a) medium, (b) medium plus corals and (c) medium plus two types of scaffolds (RCP or WCP). RNAs extracted from cells were retro-transcribed and hybridized on DNA 19.2K microarrays. No cytotoxicity was detected in corals and coral-based biopolymers. No inflammation or adverse effect was revealed by histological examination. By microarray analysis 154 clones were differentially expressed between RC and WC (81 up and 73 down regulated) whereas only 15 clones were repressed by the polymer. Histological evaluation not only confirmed that coral is a biocompatible material, but also that the polymer has no adverse effect. Microarray results were in agreement with cytological and histological analyses and provided further data regarding the genetic effects of RC, WC and the new polymer.
The measure of Quality of Life (QoL) has become one of the most important criteria used to assess the impact of chronic illness, such as asthma, on the patient’s daily life, in adults and children alike. The objective of our open observational study was to measure the QoL and analyze several factors that potentially affect QoL, such as symptoms and functional respiratory parameters, in a cohort of children with asthma. One hundred and twenty-seven children with asthma, 6 to 14 years of age, living in the city of Rome, were enrolled as outpatients. They were subjected to Skin Prick Tests (SPT), underwent spirometry and filled out the Pediatric Asthma Quality of Life Questionnaire (PAQLQ). One hundred and eleven children were diagnosed with intermittent asthma, 12 (10%) with mild asthma, and four with moderate persistent asthma. Ninety-six children had a positive SPT. The mean total score of QoL, obtained from the questionnaire, was 5.4 (±1.2 SD). Two QoL groups were created. Children with total QoL score <5.5 were included in the “Lower QoL” score group while children with total QoL score ≥5.5 were included in the “Higher QoL” score group. Children in the Higher group and their mothers had a higher mean age, suffered from fewer asthma exacerbations during the year preceding the study, and showed a higher mean value of forced expiratory volume (FEV1) compared to the children in the Lower category. Using Logistic regression we identified the main factors that may affect QoL as FEV1, symptoms in the previous year and mother’s age. QoL is correlated with the frequency of asthma exacerbations and FEV1 values. Furthermore, our research shows that a significant impairment of QoL may also occur in patients with normal lung function, pointing out the importance of evaluating QoL in all children with asthma.
The intra-articular administration of hyaluronic acid (HA) in hip osteoarthritis (OA) has been recently increased following the use of ultrasound guidance to perform an accurate delivery of the injected product. Viscosupplementation in hip OA seems to show similar results to those obtained by viscosupplementation in knee OA. However, an unmet need is the duration of symptomatic relief, therefore several new products are proposed to prolong and increase symptomatic effects. Among these, an innovative viscosupplement has been produced from high a concentration of HA combined with a high concentration of sorbitol as a free radical scavenger. The aim of this study is to evaluate the mid-term pain-relief effect of an ultrasound-guided injection of SynolisV-A (ANTI-OX-VS) in patients suffering from symptomatic hip osteoarthritis. Lequesne index, Health Assessment Questionnaire (HAQ), pain reduction, Global Patient Assessment (GPA), Global Medical Assessment (GMA) and reduction in monthly analgesic consumption were assessed during the 12-month follow-up after the injection. A total of 20 patients were enrolled in the study and received one IA US-guided injection of two syringes of ANTI-OX-VS into the target hip. Eleven drop-out patients were registered, of whom 2 were for loss of efficacy at 6 months, 1 for loss of efficacy at 9 months and 8 patients for severe comorbidities. Mean scores of all clinical parameters evaluated at each control visit were significantly different when compared with baseline mean value. No systemic adverse events were observed. Even though the sample size of this study is limited, the results suggest a durable good efficacy of a 4-ml single injection of ANTI-OX-VS in hip OA, at least for the patients who completed the study. A larger number of patients and an RCT are needed to confirm these data, investigating also the predictive factors of clinical response to ANTI-OX-VS.
LETTER TO THE EDITOR

LOCAL rhBMP-2 INJECTION AFTER DRILL-HOLE INJURY IN RATS: DOES IT HAVE SYSTEMIC EFFECTS?

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The aim of this study is to investigate the histopathological findings of drill hole healing and interactions of parathyroid hormone (PTH), β-catenin and transcription factor-4 (TCF7L2/Tcf-4) after local application of recombinant human bone morphogenic protein-2 (rhBMP-2). Sprague Dawley rats were used in two groups of ‘femoral cortex hole model’. In the non-treated group, a hole was opened with a 3 mm K-wire in the distal and mid third junction of the right femur. In the treated group, local rhBMP-2 protein was injected into the similar femoral hole. Sterile 18M H₂O was injected into the femoral hole at contralateral femur. There was more subperiosteal membranous bone reaction in the group treated with rhBMP-2 injection compared to the non-treated group. This was also proven immunohistochemically in both ipsilateral and contralateral femur with increased anti bone morphogenic protein-2 (anti BMP-2) expression. Moreover, there was an increased subperiosteal reaction at the contralateral femur. Also, in the treated group, PTH expression was increased in cells that form callus, and nuclear beta-catenin expression was increased in chondrocytes of periosteal ossification. Future studies should try to find whether the effects of rhBMP-2 on PTH and Wnt signaling pathway changes with different fracture models, also the systemic effects of local rhBMP-2 application should be investigated.
Carcinoma cuniculatum (CC) or verrucous squamous cell carcinoma is a rare variant of squamous cell carcinoma with low incidence of metastasis. It mainly affects men during the fifth-sixth decade of life, arising mostly on the weight-bearing surface of the foot, but it can also be found in other body areas. The favorable effects on the psoriatic, rheumatoid, juvenile polyarthritis as well as the ankylosing spondylitis after the application of Tumour Necrosis Factor (TNF)-alpha inhibitors, like etanercept, presume the availability of similarity between the etiopathogenetic mechanisms which are responsible for the generation of the inflammatory cascade. According to the latest studies, the sensitivity of the patients to TNF-alpha inhibitors could be genetically determined and may also be due to certain genetic polymorphisms of the NLP3 and CARD8 zones of the inflammasome. The blocking of the inflammatory reaction within the borderlines of the psoriatic arthritis could also be accepted as something of a “double-edged sword”. There is a growing volume of literary data which informs us of the clinical manifestation, not only of skin, but also of other types of tumors after the application of TNF-alpha inhibitors. This inevitably generates the hypothesis that within a certain group of patients the TNF-alpha inhibitors have some additional, and currently obscure, effects on presumably key regulatory proteins of the so-called extrinsic apoptotic pathway. Other proteins of the human inflammasome could be also implicated in the regulation of the programmed cell death and the carcinogenesis - there are speculations, that the adapter protein, ASC/TMS1, could be one of these. The present study describes the case of a patient who developed a rare form of skin tumor - epithelioma cuniculatum - whilst undergoing etanercept therapy for psoriatic arthritis. Under discussion are the possible critical connections in the complex regulatory “networks” of the inflammatory processes, the programmed cell death (apoptosis) and the carcinogenesis which, in the near or distant future, could become the objects of a targeted therapy.

Carcinoma cuniculatum in course of etanercept: blocking autoimmunity but propagation of carcinogenesis?

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LETTER TO THE EDITOR
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SALVAGE TREATMENT WITH GANCICLOVIR IN A SPLENECTOMIZED, POLYTRANSFUSED PATIENT AFFECTED BY SYSTEMIC INFLAMMATORY RESPONSE SYNDROME


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A 23-year-old man was admitted to hospital with a 12-day history of daily fever. A clinical history revealed that 10 months previously, the patient had been splenectomized and polytransfused for a severe blunt trauma. On admission, laboratory data revealed significant leukocytosis (33,230/ul). The patient's general clinical conditions rapidly worsened into a severe systemic inflammatory response syndrome in four days. After 10 days of broad-spectrum antibiotic treatment, the temperature curve was unmodified and severe leukocytosis persisted (44,300 ul) with absolute lymphocytosis. Laboratory tests ruled out hematological diseases, pneumonia, abscesses and endocarditis. In the light of IgM positivity for CMV (unconfirmed by PCR) and with the support of a PubMed search, we commenced a salvage treatment with intravenous ganciclovir, suspecting a viral infection or reactivation. After two days of therapy, an immediate defervescence was observed with a remarkable clinical improvement. After 10 days, the clinical syndrome had been completely resolved and the patient was discharged in good, general clinical health.
Skin manifestations are often associated with systemic autoimmune diseases (SAD). Some SAD, such as systemic lupus erythematosus, psoriatic arthritis and scleroderma display pathognomonic dermatological features, whereas other systemic diseases such as sarcoidosis, vasculitis and rheumatoid arthritis can present with non-specific skin manifestations that range from erythema nodosum to necrotic lesions. Here we report the case of a 25-year-old man with uveitis, polyarthritis, pulmonary involvement, nephrotic syndrome, cutaneous granuloma and pneumonia by *E. coli*.

**GRANULOMA ANNULARIS REVEALING WEGENER’S GRANULOMATOSIS**

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To assess the rate of sexual distress, sexual dysfunction and relationship quality and their association with clinical variables in women with systemic sclerosis (SSc), 102 sexually active women with SSc were recruited. Sexual distress, sexual dysfunction and dissatisfaction with relationship quality were investigated by Female Sexual Distress Scale Revised (FSDS-R), Female Sexual Function Index (FSFI) and Dyadic Adjustment Scale (DAS), respectively. The patients underwent medical examinations and nailfold videocapillaroscopy (NVC). Of the 102 patients, 37 (36%) reported sexual distress with FSDS-R score >11, 45 (44%) had sexual dysfunction with FSFI score <19 and 49 (48%) were not satisfied with relationship quality with DAS score <100. There was a negative correlation (p<0.001, R= -0.30) between FSDS-R and FSFI. No correlation was found between FSDS-R and DAS. FSFI showed a positive correlation with DAS (p<0.0001, R= 0.36). Age correlated negatively (p<0.05, R= -0.26) with FSFI, while FSDS-R and DAS did not correlate (p>0.05) with age. SSc women with digital ulcers (DU) had a reduction of FSFI and DAS compared with women without DU. In patients with late capillaroscopic pattern, mean value of FSFI was significantly lower than the other two capillaroscopic patterns. DAS decreased with progression of capillaroscopic damage. In a high percentage of women with SSc FSDS-R was increased, while FSFI and DAS were reduced. Age correlated negatively with FSFI, while skin score showed a negative correlation with DAS. Digital vascular damage negatively influenced FSFI and DAS.
LETTER TO THE EDITOR

EXCIMER UV RADIATION IN DERMATOLOGY

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Ultraviolet B (UVB 290-320 nm) radiation has been used in the treatment of different skin diseases. Light sources with narrowband UVB output spectrum have been developed with the aim of increasing the rates of “beneficial to side effect” profile of the treatment. Narrowband UVB phototherapy using fluorescent lamps (TL01, 311±2nm) has been widely adopted over the past 10 years. Monochromatic Excimer Light (MEL) represents a new source of narrow-band UVB emitting at 308 nm and guarantees a safe and effective approach to different chronic and recurrent skin diseases thanks to its potent and selective immunosuppressant action.
LETTER TO THE EDITOR

MODULATION OF POLYFUNCTIONAL HIV-SPECIFIC CD8 T CELLS IN PATIENTS RESPONDING DIFFERENTLY TO ANTIRETROVIRAL THERAPY


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Antiretroviral therapy allows a restoration of immune cell homeostasis associated with a normal immune competence. Our goal was to analyze the modulation of polyfunctional HIV-specific CD8+ T-cell responses during antiretroviral therapy. HIV-infected individuals were divided into four groups according to CD4+ cell count and viral load at the moment of recruitment. Whole blood was stimulated with a pool of CD8-specific HIV-antigens to assess cytokine/chemokine production and cytotoxicity activity by using flow cytometry. The groups show different modulation in HIV-specific CD8+ T-cell responses. In particular, immunological failure showed different distributions of polyfunctional HIV-specific CD8+ responses, mainly due to an increase of cells producing CD107a/IFNγ/IL-2/MIP-1β. Our results indicate that this particular 4+ functional subset is a possible correlate of immunological failure. Considering the complexity of interactions among HAART, immune system and HIV, work is in progress to find correlates of therapy efficacy.
Churg-Strauss (CSS) syndrome is rare and of unknown etiology. It is associated with vasculitis, blood eosinophilia and granulomatosis, and affects multiple organs and systems at various stages of the disease. Specific diagnostic and monitoring tests are not yet available. This study aims to assess the changes in MMP-2 and MMP-9 along with the histopathological alterations in two cases of CSS, as possible potential diagnostic and monitoring criteria. Two adult male patients were diagnosed with CSS in the otorhinolaryngology clinic in the University of Palermo, based on multiple clinical and histopathologic criteria. Biopsies of respiratory mucosa were taken after the consent of the patients, processed for routine histopathology and immunohistochemistry as well as quantitative polymerase chain reaction (qPCR). Similar biopsies were also taken from a non-CSS patient. The Assessment of MMP-2 and MMP-9 was performed using both immunohistochemistry and qPCR techniques. Histopathological alterations in the respiratory mucosa were consistent with vasculitis and granulomatous tissue formation, in addition to inflammatory cell infiltration with abundance of eosinophils. Immunohistochemistry assay performed on the samples derived from the two CSS patients showed a relative and remarkable increase of both MMP-2 and MMP-9 compared to controls. Such an increase was consistent with the qPCR results which depicted a significant increase between 20 and 30% for both MMP-2 and MMP-9, respectively. Since the secretion of MMPs is an essential step in angiogenesis, could these enzymatic factors be used as parameters to diagnose or monitor the evolution of CSS? The small number of samples analyzed in this study does not allow us to suggest a general statement correlating the increase in expression of MMP-2 and MMP-9 to the appearance or evolution of vasculitis; it is only speculative.
LETTER TO THE EDITOR

SAFETY AND INFECTIOUS PROPHYLAXIS OF INTRAVENOUS IMMUNOGLOBULIN IN ELDERLY PATIENTS WITH MEMBRANOUS NEPHROPATHY

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A variety of infections has been recognized as an important cause of morbidity and mortality in patients with nephrotic syndrome, and membranous nephropathy is a common cause of this in the elderly. The reasons for infection risk are due to oedema complications, urinary loss of factor B and D of the alternative complement pathway, cellular immunity, granulocyte chemotaxis, hypogammaglobulinemia with serum IgG levels below 600 mg/dL, and secondary effects of immunosuppressive therapy. Many different prophylactic interventions have been used for reducing the risks of infection in these patients but recommendations for routine use are still lacking. We report two membranous nephropathy cases in the elderly in which Intravenous immunoglobulin were useful in long-term infectious prophylaxis, showing safety in renal function. During immunosuppressant therapy in membranous nephropathy, intravenous immunoglobulin without sucrose are a safe therapeutic option as prophylaxis in those patients with nephrotic syndrome and IgG levels below 600 mg/dL. The long-term goal of infection prevention in these patients is to reduce mortality, prolong survival and improve quality of life.
LETTER TO THE EDITOR

MULTIPLE PULMONARY NODULES AND UNEXPLAINED FEVER:
WHEN THE PULMONOLOGIST FAILS

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We describe herein a difficult case of persistent and refractory fever, associated with multiple lung nodules, progressive respiratory failure and general deterioration. Our patient was carefully investigated for the possible causes of his symptoms, using current and advanced diagnostic procedures, either serological or by imaging. The confirmatory diagnosis of anaplastic T-cell lymphoma, was obtained only after an invasive procedure (with severe pneumothorax), although it was too late. This suggests that also very rare diseases should be considered in the presence of unexplained signs/symptoms, and that in such cases, aggressive diagnostic procedures should be applied as early as possible.