EDITORIAL

REVIEW ON MEDICINAL USES, PHARMACOLOGICAL, PHYTOCHEMISTRY AND IMMUNOMODULATORY ACTIVITY OF PLANTS

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Since ancient times, plants have been an exemplary source of medicine. Researchers have discovered some important compounds from plants. The present work constitutes a review of the medicinal plants whose immunomodulant activity has been proven. We performed PUBMED, EMBASE, Google scholar searches for research papers of medicinal plants having immunomodulant activity. Medicinal plants used by traditional physicians or reported as having immunomodulant activity include Acacia concinna, Camellia sinensis, Lawsonia inermis Linn, Piper longum Linn, Gelidium amansii, Petroselinum crispum, Plantago major and Allium sativum. Immunomodulant activities of some of these medicinal plants have been investigated. The medicinal plants documented have immunomodulant activity and should be further investigated via clinical trial.
THE “MYSTERY” OF CUTANEOUS SARCOIDOSIS: FACTS AND CONTROVERSIES

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The reason why the cutaneous form of sarcoidosis is well known in the literature is because of its spectrum of manifestations granting it the fame of a Great Imitator. The mystery shrouding the pathogenesis of this rare cutaneous disease is still there (in spite of the fundamental progress of the various diagnostic methods in current day medicine). The production of the morphological substrate – the epithelioid cell granuloma – which is considered to be characteristic of skin sarcoidosis, could, however, also be the end result of a reaction to i) various specific infectious agents such as Leishmaniasis cutis, coccidioidomycosis, etc., ii) certain residual bacterial or other mycobacterial antigens which, at the moment of setting the diagnosis are - by definition - non-infectious but still immunogenic, as well as iii) different tumor antigens in lesional tissue or other location. Often, differentiating between sarcoidosis and a sarcoid-like reaction, based on the updated criteria for cutaneous sarcoidosis, is problematic to downright impossible. A future characterization of the genetic signature of the two conditions, as well as the implementation of additional mandatory panels for i) the identification of certain infectious or ii) non-infectious but immunogenic and iii) tumor antigens in the epithelioid cell granuloma (or in another location in the organism), could be a considerable contribution to the process of differentiating between the two above-mentioned conditions. This will create conditions for greater accuracy when setting the subsequent therapeutic approaches.
Mast cells (MCs) derive from a distinct precursor in the bone marrow and are predominantly found in tissues at the interface between the host and the external environment where they can secrete mediators without overt degranulation. Mast cells mature under local tissue microenvironmental factors and are necessary for the development of allergic reactions, through crosslinking of their surface receptors for IgE (FcεRI), leading to degranulation and the release of vasoactive, pro-inflammatory and nociceptive mediators that include histamine, pro-inflammatory and anti-inflammatory cytokines and proteolytic enzymes. Multiple sclerosis (MS) is an autoimmune disease characterized by inflammatory demyelination within the central nervous system. MCs are involved in the pathogenesis of MS by generating various vasoactive mediators and cytokines and participate in the destruction of the myelin sheath and the neuronal cells. The process of the development of demyelinating plaques in MS is probably linked with the rupture of the blood–brain barrier by MC products. The effects of natalizumab, which is a very effective drug in reducing the annualized relapse rate and other relapse-based endpoints, are discussed. Here, we report the relationship between MCs and MS.
Cancer stem cells possess the qualities of self-renewal, tumorigenesis and the ability to recapitulate a heterogeneous tumor. Our group was the first to isolate head and neck squamous cell carcinoma (HNSCC) stem cells using the cell surface marker CD44. CD44 is a trans-membrane glycoprotein with a multitude of key-functions that regulate cancer cell proliferation and metastasis. The variety of CD44 functions is due to tissue-specific patterns of glycosylation of the extracellular portion, and to the multiple protein isoforms (CD44 variants, CD44v) generated by alternative splicing. This study investigates the expression pattern of CD44 variants in HNSCC. Ten cell lines from the most common HNSCC locations and representative of various clinical outcomes were assayed by quantitative real-time PCR, flow cytometry and immunofluorescence comparatively with normal oral keratinocytes. The CD44 v4 and v6 were exclusively abundant in HNSCC while the isoform v1,2 was expressed in normal oral keratinocytes. Of interest, the highest level of CD44v6 expression was detected in advanced metastatic HNSCC, suggesting a link between CD44v6 expression and HNSCC metastasis, while the highest CD44v4 was detected in a stage IV HNSCC refractory to chemotherapy which developed recurrence. Oral-derived HNSCC expressed the highest CD44v4 and v6, and levels corresponded with staging, showing also an increasing tendency with recurrence and metastasis. CD44v were detected predominantly in smaller cells (a characteristic that has been associated with stem cell properties) or cells with mesenchymal morphology (a characteristic that has been associated with the migratory and invasive potential of epithelial tumor cells), suggesting that CD44v differential expression in HNSCC may be representative of the morphological changes inherent during tumor progression towards a more aggressive potential, and thus contributing to the individual tumor biology. The mechanism of CD44 variant involvement in HNSCC progression and metastasis is under investigation.
EFFECT OF AN EDUCATIONAL PROGRAM IN PRIMARY CARE: THE CASE OF LIPID CONTROL IN CARDIO-CEREBROVASCULAR PREVENTION

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Lowering blood cholesterol levels reduces the risk of coronary heart disease. However, the effect of interventions depends on the patients’ adherence to treatment. Primary care plays an important role in the detection, treatment and monitoring of disease, therefore different educational programs (EP) have been implemented to improve disease management in general practice. The present study is aimed to assess whether a general practitioner auditing and feedback EP may improve dyslipidaemia management in a primary care setting and to evaluate patients’ adherence to prescribed lipid-lowering treatment. The quality of cardiovascular and cerebrovascular disease prevention before and after the implementation of an EP offered to 25 general practitioners (GPs), was evaluated. Clinical and prescription data on patients receiving at least one lipid-lowering treatment was collected. To evaluate the quality of the healthcare service provided, clinical and biochemical outcomes, and drug-utilization, process indicators were set up. Adherence was evaluated before and after the EP as the “Medication Possession Ratio” (MPR). A correlation analysis was carried out to estimate the effect of the MPR in achieving pre-defined clinical end-points. Prescription data for lipid-lowering drugs was collected in a sample of 839 patients. While no differences in the achievement of blood lipid targets were observed, a slight but significant improvement of the MPR was registered after the EP (MPR >0.8=64.2% vs 60.6%, p=0.0426). Moreover, high levels of statin adherence were associated with the achievement of total blood cholesterol target (OR=3.3 for MPR >0.8 vs MPR <0.5, 95% CI:1.7-6.7) or LDL therapeutic goal (OR=3.3 for MPR >0.8 vs MPR <0.5, 95% CI:1.5-7.2). The EP partially improved the defined clinical targets; probably, a more patient-based approach could be more appropriate to achieve the defined target. Further studies are needed to identify how healthcare services can be improved.
CHANGES IN EXTRA- AND INTRACELLULAR pH IN HEPATOCYTES EXPOSED TO GABEXATE MESILATE

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Gabexate mesilate (GM) is a synthetic inhibitor of plasmatic and pancreatic serine proteases licensed for the treatment of pancreatitis. Here we show that in suspensions of isolated hepatocytes, profound changes in extracellular, cytoplasmic, and vesicular pH occur after addition of GM. Isolated hepatocytes obtained by collagenase perfusion of rat liver were pre-incubated with 1, 2, and 4 mM GM. Extracellular pH (pH in the incubation medium) was measured by a conventional pH electrode, cytosolic and vesicular pH were measured by fluorescence changes of 2',7'-biscarboxyethyl-5,6-carboxyfluorescein acetoxymethyl ester (BCECF-AM) and fluorescein dextran, respectively. Incubation of hepatocytes with GM resulted in a dose-dependent decrease of extracellular pH. Cytosolic pH decreased rapidly and markedly in a dose-dependent manner during the first minutes and gradually returned towards baseline. Simultaneously, GM induced a rapid alkalinization of acidic vesicles. The presence of bis-(p-nitrophenyl) phosphate (BNPP), an esterase inhibitor, reduced the extent of extracellular acidification. Incubation of hepatocytes with GM resulted in a dose-dependent decrease of extracellular pH. Cytosolic pH decreased rapidly and markedly in a dose-dependent manner during the first minutes and gradually returned towards baseline. Simultaneously, GM induced a rapid alkalinization of acidic vesicles. The presence of bis-(p-nitrophenyl) phosphate (BNPP), an esterase inhibitor, reduced the extent of extracellular acidification. Incubation of hepatocytes in the presence of dimethylamiloride, an Na⁺/H⁺ exchanger inhibitor, or in a sodium-free medium, did not modify the rate and extent of extracellular acidification. GM, a commercially available pharmacological agent, could be useful to manipulate extra- and intracellular pH.
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) is a well-defined syndrome in which tics (motor and/or vocal) and/or obsessive compulsive disorders (OCD) consistently exacerbate in temporal correlation to a Group A beta-haemolytic streptococcal infection. In children with PANDAS, there is speculation about whether tonsillectomy or adenotonsillectomy might improve the neuropsychiatric course. Our objective was to examine whether such surgery impacted remission or, in patients without remission, modified clinical course of the disease, streptococcal antibody titers, neuronal antibodies or clinical severity of Obsessive-Compulsive Disorder (OCD) and/or tics.

Study participants (n = 120) with positive PANDAS criteria were recruited, examined, and divided into surgical or non-surgery groups. The surgical group consisted of children with tonsillectomy or adenotonsillectomy (n=56). The remaining children were categorized as non-surgery (n=64). Clinical follow-up was made every 2 months for more than 2 years. Surgery did not affect symptomatology progression, streptococcal and neuronal antibodies, or the clinical severity of neuropsychiatric symptoms in these children. In conclusion, in our series clinical progression, antibody production, and neuropsychiatric symptom severity did not differ on the basis of surgical status. We cannot uphold surgical management as likely to impact positive remission rates, course of OCD/tics, or antibody concentrations in children with PANDAS.
OZONE AUTOHEMOTHERAPY INDUCES LONG-TERM CEREBRAL METABOLIC CHANGES IN MULTIPLE SCLEROSIS PATIENTS

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Ozone autohemotherapy is an emerging therapeutic technique that is gaining increasing importance in treating neurological disorders. A validated and standard methodology to assess the effect of such therapy on brain metabolism and circulation is however still lacking. We used a near-infrared spectroscopy (NIRS) system to monitor the cerebral metabolism and a transcranial Doppler (TCD) to monitor the blood flow velocity in the middle cerebral arteries. Fifty-four subjects (32 neurological patients and 22 controls) were tested before, during, and after ozone autohemotherapy. We monitored the concentration changes in the level of oxygenated and deoxygenated haemoglobin, and in the level of the Cytochrome-c-oxidase (CYT-c). As a primary endpoint of the work, we showed the changes in the brain metabolism and circulation of the entire population. The concentration of oxygenated hemoglobin increased after the reinjection of the ozoned blood and remained higher than the beginning for another 1.5 hours. The concentration of the deoxygenated haemoglobin decreased during the therapy and the CYT-c concentration markedly increased about 1 hour after the reinjection. No significant changes were observed on the blood flow velocity. As secondary endpoint, we compared the NIRS metabolic pattern of 20 remitting-relapsing multiple sclerosis (MS) patients against 20 controls. We showed that by using only 7 NIRS variables it was possible to characterize the metabolic brain pattern of the two groups of subjects. The MS subjects showed a marked increase of the CYT-c activity and concentration about 40 minutes after the end of the autohemotherapy, possibly revealing a reduction of the chronic oxidative stress level typical of MS sufferers. From a technical point of view, this preliminary study showed that NIRS could be useful to show the effects of ozone autohemotherapy at cerebral level, in a long-term monitoring. The clinical result of this study is the quantitative measurement of the CYT-c level changes in MS induced by ozone autohemotherapy.
The possible use of cell therapies for neurological lesions and disorders is regarded as a very promising strategy. However, many issues related to cell type, tissue donor, expected biological action etc., are still open. In this study human mesenchymal stem cells derived from different fetal and adult tissues were examined in order to explore growth and neurotrophic factor synthesis and biological action, also considering the individual variability of the donors. Cells were derived from different human tissues and characterized according to the guidelines of the International Society for Cellular Therapy. Growth and neurotrophic factor synthesis was evaluated by real time PCR, biological assays and ELISA. It was found that human mesenchymal stem cells produce vascular endothelial-, nerve-growth factor (VEGF, NGF), brain-derived-, ciliary- and glial-derived neurotrophic factors (BDNF, CDGF, GDNF), which are neuroprotective molecules, but the source and the donor influence the synthesis rate. Accordingly, it is suggested that the source and the individual variability are key issues to be considered in the perspective of the clinical use of mesenchymal stem cells in neurological disorders.
AN ANTIBODY REACTIVITY-BASED ASSAY FOR DIAGNOSIS OF INVASIVE CANDIDIASIS USING PROTEIN ARRAY

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The increased incidence of invasive candidiasis and of patients at risk requires early diagnosis and treatment to improve prognosis and survival. The aim of this study was to set up a ten-protein array-based immunoassay to assess the IgG antibody responses against ten well-known immunogenic C. albicans proteins (Bgl2, Eno1, Pgk1, Pdc11, Fba1, Adh1, Als3, Hwp1, Hsp90 and Grp2) in 51 patients with invasive candidiasis (IC) and in 38 culture-negative controls (non-IC). Antibody levels were higher against Bgl2, Eno1, Pgk1, Als3, Hwp1 and Grp2, than against Adh1, Pdc11, Fba1 and Hsp90, irrespectively of the patient group considered. Moreover, the IgG levels against Bgl2, Eno1, Pgk1 and Grp2 were significantly higher in IC than in non-IC patients. Furthermore, the ROC curves generated by the analysis of the antibody responses against Bgl2, Grp2 and Pgk1 displayed AUC values above 0.7, thus discriminating IC and non-IC patients. According to these results, the employment of the microarray immunoassay (a rapid, sensitive and multiparametric system), in parallel with conventional diagnostics, can help to spot IC patients. This ultimately will allow to initiate an early, focused and optimized antifungal therapy.
Acute respiratory infections (ARI) still represent a big challenge for paediatricians, especially in those children defined as “ailed” as they are more susceptible to such kinds of disease. In this paediatric population, the immune system is still under-developed with an evident alteration in cytokine levels. A clinical study was carried out in 5 sites in Russia with the intention to enrol children particularly susceptible to contract respiratory infections (defined as “ailing”), assigning them to a treatment group with pidotimod in comparison with a control group, treating them for 30 days and observing the reduction in the number of ARI episodes throughout the follow-up period (6 months). Moreover, changes in serum immunological markers were evaluated at baseline and 30 days after treatment discontinuation. One hundred and fifty-seven ailing children were enrolled and assigned to two arms: a main pidotimod-treatment group or a control group. The percentage of incidence of ARIs in the observation period at three different time points was statistically significant (p < 0.05). At the end of the follow-up period (after 6 months), ARIs had developed in 72 children (92.3%) in the main group and in 79 patients (100%) in the control group. Concerning changes of the immunological markers, the treatment group showed a better profile of normalization compared to the control group. The 30-day pidotimod therapy course led to improvement/reduction in the rate of acute respiratory infection recurrence in ailing children within a 3-month period, with a quick elimination of symptoms and signs of infection and, as a result, a faster recovery. The normalisation of the content of the pro-inflammatory cytokine interleukin-8 confirmed the immune-modulatory effect of the investigational drug, underlying its prophylactic effect.
LETTER TO THE EDITOR

DO ELEVATED SERUM IgM LEVELS HAVE TO BE INCLUDED IN PROBABLE DIAGNOSIS CRITERIA OF PATIENTS WITH ATAXIA-TELANGIECTASIA?

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Ataxia-telangiectasia (AT) is a rare multisystem, neurodegenerative genetic disorder that is characterised by progressive neurological abnormalities, oculocutaneous telangiectasias and immunodeficiency. Delay in diagnosis or misdiagnosis is probable due to its wide clinical heterogeneity in infancy. Recurrent sinopulmonary infections are often the only presenting symptom and usually patients have decreased immunoglobulins. A total 10% of patients who present with decreased serum immunoglobulin G and A and with normal or elevated immunoglobulin M levels are often misdiagnosed as hyperimmunoglobulin M syndrome. Definitive diagnosis is made if a patient with progressive cerebellar ataxia has a disease causing mutation on the ATM gene. Ataxia-telangiectasia guideline of the European Society for Immunodeficiencies defines the probable diagnosis criteria. We evaluated twenty ataxia-telangiectasia patients (mean age 13.8±4.1 years) retrospectively who were followed-up for a mean of 38.6±27.0 months. Twelve patients had a family history of consanguinity. A total of 80% patients suffered from various infections. Neoplasms occurred in three of them. Patients showed immunological abnormalities as low IgG (45%), low IgA (65%) and elevated IgM (60%) levels. CD3⁺CD4⁺ T lymphocyte frequency was low in 45% patients. The mean AFP concentration at the diagnosis was 191.9±140.1 ng/mL and the raised IgM values did not show any statistically significant relationship with high AFP concentrations. Frequency of the elevated IgM concentrations in (60%) patients raises the concerns about thinking this finding has to be accepted as a probable diagnosis criterium.
LETTER TO THE EDITOR

RECURRENT MISCARRIAGES IN WOMEN NOT FULFILLING CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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Obstetric antiphospholipid antibody syndrome (APS), is well defined by classification criteria. It is well known that women with APS should receive prophylactic anticoagulation therapy with subcutaneous low weight heparin all throughout pregnancy and in the first 6 weeks postpartum. However, the optimal treatment for pregnant women having positive anti-phospholipid antibodies, but not fulfilling classification criteria for APS is still unclear. In this retrospective study we report pregnancy outcomes of 10 patients affected by recurrent miscarriages and positive anti-cardiolipin or aβ2GP1 antibodies with titers ranging from 10 to 20 GPL/MPL demonstrated at least twice before pregnancy.
Overweight and obesity are the fifth leading risk for global deaths and its prevalence has doubled since 1980. At least 2.8 million adults, worldwide, die each year as a result of being overweight or obese. The deleterious effects of obesity are tightly related to diabetes, as they are often clinically present in combination to confer increased cardiovascular mortality. Thus, patients with diabetes and obesity are known to develop accelerated atherosclerosis characterized by a dysfunctional endothelium and decreased nitric oxide bioavailability. Recent clinical studies support, indeed, the use of incretin-based antidiabetic therapies for vascular protection. Thus, attention has been focusing on gut hormones and their role, not only in the regulation of appetite but also in vascular health. Intervention directed at modulating these molecules has the potential to decrease mortality of patients with diabetes and obesity. This review will cover part of the ongoing research to understand the role of gut hormones on endothelial function and vascular health.

GUT HORMONES AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH OBESITY AND DIABETES

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LETTER TO THE EDITOR

NOVEL HYDROXYAPATITE BIOMATERIAL COVALENTLY LINKED TO RALOXIFENE

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Since raloxifene, a drug used in osteoporosis therapy, inhibits osteoclast, but not osteoblast functions, it has been suggested to improve recovery during implant surgery. The present paper describes an effective method to link raloxifene, through a covalent bond, to a nano-Hydroxyapatite-based biomaterial by interfacing with (3-aminopropyl)-Triethoxysilane as assessed by Infra Red-Fourier Transformed (IR-FT) spectroscopy and Scanning Electron Microscope (SEM). To evaluate the safety of this modified new material, the vitality of osteoblast-like cells cultured with the new biomaterial was then investigated. Raloxifene-conjugated HA-biomaterial has been shown to be a safe material easy to obtain which could be an interesting starting point for the use of a new functional biomaterial suitable in bone regeneration procedures.
Behçet’s disease (BD) is a multi-systemic vasculitis characterized by the possible presence of cutaneous, ocular, articular and neurological manifestations. In this report, we examine the case of a fifteen-year-old boy with an incomplete form of juvenile Behçet’s disease which began with joint involvement and developed into a complete form only after several years. The patient showed a rapid response to anti-TNF-alpha (infliximab) with an improvement of mucocutaneous lesions (oral and genital ulcers, pseudofolliculitis) and arthritis.
Primary Snoring (PS) has been positioned at the milder end of the Sleep-Disordered Breathing severity continuum characterized by snoring and it is usually underestimated. PS is defined as snoring without apnea, frequent arousals, or gas exchange abnormalities and recent studies demonstrated that children with PS have increased blood pressure and reduced arterial distensibility. The association between adipokines and SDB has been recently investigated, though most of the studies were focused on OSAS where intermittent hypoxia characterizing the disease may lead to an inflammatory cascade and to the release of several adipokines, contributing to oxidative stress. Resistin, initially described as an adipokine increasing insulin resistance, has been recently identified as a novel important member of the cytokine family involved in the regulation of inflammation. The aim of our study was to investigate circulating resistin levels in normal weight children with PS. Sixty-five children of normal weight aged between 4 and 14 years of age were selected for habitual snoring. Children with positive polysomnography were excluded from the study. Serum resistin levels were detected in all children with PS. Thirty-three healthy non-snorer children with similar age, sex and BMI were selected as a control group. A significantly higher level of resistin was observed in patients with PS compared to the control group (4.67±1.91 ng/ml vs 3.98±1.58 ng/ml; p<0.01). Patients with inconclusive pulse oximetry showed significantly higher resistin levels than those with negative recordings (5.29±1.91 ng/ml vs 4.20±1.93 ng/ml; p<0.008). Moreover, there was a significant increasing trend between sieric adipokine level and the frequency of snoring (p=0.006). Our results suggest that systemic inflammation and oxidative stress may also play a significant role in the pathophysiology of PS.
LETTER TO THE EDITOR

RETROSPECTIVE OBSERVATIONAL STUDY TO INVESTIGATE SINERGA, A MULTIFACTORIAL NUTRITIONAL PRODUCT, AND BACTERIAL EXTRACTS IN THE PREVENTION OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN

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In this retrospective observational clinical study, 167 children, aged 3 to 7 years, of both sexes, with a clinical history of recurrent respiratory infections, administered with bacterial extracts of first and second generation or Sinerga a nutritional product containing palmitoylethanolamide, bovine colostrum, phenylethylamine and the new generation of probiotic kluyveromyces FM B0399, were observed. The goal of the study was to compare the supplementation with Sinerga with the supplementation with bacterial extracts, for the effect on the frequency of episodes of respiratory infection that had resulted in a prescription for antibiotics. The study focused retrospectively on the months from March 2013 to November 2012. The results showed a greater reduction in the frequency of respiratory infections with antibiotic therapy in the group of children supplemented with Sinerga than in the group treated with bacterial extracts. In particular, it was observed that 49.3% of the children supplemented with Sinerga, against 5% of those supplemented with extracts, had no infectious episodes requiring the administration of an antibiotic. 100% of subjects supplemented with Sinerga have had no more than two episodes of respiratory infection, while this condition, in the cohort treated with bacterial extracts, was observed in only 51% of cases.
Extranodal non-Hodgkin lymphomas limited to the larynx are rare, accounting for less than 1% of all laryngeal neoplasms. The most common site of development of primary laryngeal lymphomas is the supraglottic region. In most cases, the presenting symptoms are hoarseness, dysphagia, dyspnea, and cervical lymphadenopathy. They consist mainly of non-Hodgkin lymphoma, especially of diffuse large B-cell lymphoma and mucosa-associated lymphoid tissue. We report a case of a primary extranodal marginal zone of mucosa-associated lymphoid tissue (Malt Lymphoma) of the larynx in a 73-year-old non-smoker woman, presented as chronic cough, unresponsive to oral corticosteroid. We present a detailed report of her clinical and paraclinical data as well as treatment options. In patients with chronic cough, uncommon causes should be considered when the cough persists after evaluation for common causes. If a cough persists after consideration of the most common causes, CT scan and a bronchoscopic evaluation are fundamental for the diagnosis of tumors of the upper and lower respiratory tract.