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LUNG MICROBIOME: PATHOGENESIS AND PROGRESSION OF PID

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The term microbiome is commonly used when referring to the complex community of microbes that inhabit a specific body site. Only 5% of microorganisms are currently cultivable and new applications of culture-independent techniques of microbial identification revealed diverse communities of microbes in the lung in both diseased patients and healthy subjects. The construction of the respiratory microbiome is a consequence of microbial immigration, microbial elimination, and the relative reproduction rates of its members. Numerous factors may influence the composition of the microbiome: environmental factors (smoking, pollution), host factors (allergic reactions, infections), drugs (antibiotics, corticosteroids, and immunosuppressants), and pulmonary injury. It is not clear whether an altered lung microbiome contributes to disease pathogenesis or it is only a marker of injury and inflammation. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and lethal fibrosing interstitial lung disease of unknown etiology, characterized by a poor prognosis. The patients with IPF had a significantly higher bacterial burden than subjects with chronic obstructive pulmonary disease and than healthy control subjects. The subjects with idiopathic pulmonary fibrosis with the highest bacterial load were at increased risk of mortality when compared with subjects with IPF with the lowest bacterial burden. Individuals with IPF whose disease had progressed at 6 months demonstrated a significantly higher BAL bacterial burden when compared with subjects with stable disease. The potential role of the microbiome in the pathogenesis of idiopathic pulmonary fibrosis could support further investigation of the role of antibiotics as a potential therapeutic approach.

Keywords: idiopathic pulmonary fibrosis, pathogenesis, microbiome, BAL bacterial burden

COMORBIDITIES IN IPF: ASSOCIATIONS, CAUSES, CONSEQUENCES?

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Idiopathic pulmonary fibrosis (IPF) is a severe, progressive and debilitating disease with a median survival period of 2-3 years after diagnosis. A high rate of comorbidities was documented in IPF, illustrating the difficulty in treating this vulnerable patient group. Multiple comorbidities, including gastroesophageal reflux disease, venous thromboembolism, coronary artery disease, sleep-disordered breathing, depression, emphysema, pulmonary hypertension and lung cancer contribute to the morbidity and mortality of IPF patients. Combined pulmonary fibrosis and emphysema (CPFE) is increasingly recognized, but its prevalence and prognosis remain unclear. The development of pulmonary hypertension in IPF is associated with worsened functional status and significantly decreased survival. Abnormal acid gastro-oesophageal reflux is highly prevalent and represents an important risk factor for IPF development or progression. Obstructive sleep apnea (OSA) is prevalent in patients with IPF and is underdiagnosed; formal sleep evaluation and polysomnography should be considered as part of the management strategy. There is a higher prevalence of coronary artery disease in IPF patients compared with the general population, although this increased association appeared to be independent of common coronary artery risk factors. The awareness of the specific comorbid conditions that are present in IPF patients is important as detection and treatment of comorbid conditions may have a clinically significant and meaningful impact on overall outcomes in patients with IPF. In the absence of efficient treatment options for the majority of patients diagnosed with IPF, this may play a role in the effort to optimize the survival of IPF patients.

Keywords: idiopathic pulmonary fibrosis, co-morbidities, gastro-esophageal reflux, obstructive sleep apnea, combined pulmonary fibrosis and emphysema

EVOLUTION AND PROGNOSIS OF INTERSTITIAL LUNG DISEASES

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The paper reviews the literature data on evolutive and prognostic particularities of patients diagnosed with Idiopathic Interstitial Pneumonias (IIPs), based on clinical-imagistic and histopathological aspects. A literature review regarding the Idiopathic Interstitial Pneumonias (IIPs) was performed. Over the past 15 years, there has been a continuing interest in identifying and describing as accurately as possible the clinical patterns in correlation with imaging and histopathology aspects in interstitial lung diseases (ILD). The evolution and prognosis are directly related to the etiology and type of ILD, idiopathic pulmonary fibrosis (IPF) having by far the shortest survival and bad prognosis. The evolution and prognostic particularities of patients diagnosed with Idiopathic Interstitial Pneumonias (IIPs) depend on clinical-imagistic and histopathological aspects, a correct diagnosis sustained by a multidisciplinary team being essential. The presentation takes into consideration the possible factors that influence the evolution of IIPs. The introduction of new drugs (pirfenidone and nintedanim), which have shown a positive impact on the decline in vital forced capacity (FVC) and increase survival in patients with IPF in clinical trials, brings hope for these patients.

Keywords: idiopathic interstitial pneumonias, evolution, prognosis

CHALLENGES AND DIAGNOSTIC ERRORS IN INTERSTITIAL LUNG DISEASES

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Interstitial lung diseases (ILD) define a complex pathologic category of pulmonary conditions including over 200 entities that modify the pulmonary function. All these conditions have similarities, are difficult to distinguish with basic clinical expertise and their unique properties require a keen sense of diagnostic from the clinician, as well as a complex battery of clinical investigations. One of the most frequent error that a clinician must avoid is the terminology misuse. The general term of "interstitial pulmonary fibrosis" or "diffuse pulmonary fibrosis" is wrong in its essence – as "fibrosis" is a separate condition, not all the interstitial pneumopathies necessarily evolve towards fibrosis and does not include a huge pool of other interstitial conditions (such as alveolities, granulomatosis, eosinophilic pneumopathies etc.) But the terminology itself has changed throughout the years. The joined ATS/ERS multidisciplinary consensus proposed in 2002 a guideline to describe and diagnose these conditions. The terminology used was "diffuse parenchymal lung diseases" and belonging to this group the "idiopathic interstitial pneumonias" (IIP) defined 7 specific conditions: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP). This classification was redefined in 2013 with the publication of *the Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias*, changing the classification and the terminology and defining the clinical and histopathological terms of diagnostic. The new classification included *Major idiopathic interstitial pneumonias*, *Rare idiopathic interstitial pneumonias* and *Unclassifiable idiopathic interstitial pneumonias*. The most common diagnostic errors are related to symptomatology and the highly unspecific signs and symptoms, the interpretation of imagistic data and pulmonary function testing. The histopathological analysis, although a mean of certitude in considering the tissue modifications, may not be available in all situations. The HRCT images are typical for diagnostic in only 50% of the cases and the lack of lung biopsy in case of clinical and imagistic major discordance may lead to an erroneous diagnostic. In many cases, the diagnostic is biased, delayed or mislead by using steroid therapy prescribed too soon and with too little clinical data to support it. In 2015, The Pulmonary Fibrosis Foundation (PFF) commissioned the Interstitial Lung Disease Patient Diagnostic Journey (INTENSITY) survey that interviews 600 patients (300 men and 300 women) with a 25-minute online questionnaire and the results showed that 55% were misdiagnosed. 49% of the respondents carried a wrong diagnostic for a period of 1 to 10 years and 38% were misdiagnosed more than twice with allergies, asthma etc. The median time from the onset of symptoms to the diagnostic and therapeutic attitude was 11 months. In conclusion, the diagnosis of interstitial lung diseases is a complex process starting with physician's ability to evoke the disease in the epidemiological, clinical and onset context and ending with interdisciplinary effort of a team of experts, combined with solid medical knowledge and paraclinical equipment. If possible, the lung biopsy may bring an added value to the quality of diagnostic, but can also be ruled out by following the guidelines and having adequate HRCT interpretation and biological markers at hand. Long delays in diagnostic of ILD and the barriers set by lacking biomarkers, HRCT quality, early steroid medication or incomplete evaluation of differential diagnostics may lead to errors in diagnostic and patient harm, and also increased costs for the healthcare systems and the patients.

Keywords: diagnostic errors, interstitial lung disease diagnostic, ILD diagnostic error

WHAT'S HOT IN CRYOTECHNOLOGY?

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Cryotechnology has been used in treating lung cancer for many years, and now it is emerging to have a new indication in diagnosing lung diseases. Cryoprobe transbronchial lung biopsy has been introduced into clinical practice as a new technique, providing a larger biopsy specimen, potentially improving the diagnostic yield of transbronchial biopsies in parenchymal lung diseases. Diffuse parenchymal lung diseases (PID) are a heterogeneous group of over 200 pulmonary disorders that contribute to diffuse and often patchy involvement of the bilateral lung parenchyma. A multidisciplinary approach to PID is critical. Histology is a key element for diagnosis of fibrotic diffuse parenchymal lung diseases PID and particularlly in idiopathic pulmonary fibrosis (IPF), when the clinical-radiological picture is nondiagnostic. Surgical lung biopsies SLB have been long considered the gold standard for the diagnosis of PID. However, not all patients can safely undergo surgery due to respiratory impairment and medical co-morbidities. Bronchoscopic lung cryobiopsies may fit into the diagnostic algorithm of PID. Cryobiopsy is safe, has a high diagnostic yield and has lower complication and mortality rates compared to SLB. Cryobiopsy might be considered the first diagnostic approach for obtaining tissue in ILDs.

Keywords: cryobyopsy, diffuse parenchymal lung diseases (PID), idiopathic pulmonary fibrosis (IPF)

A SEPARATE ENTITY: COMBINED IDIOPATHIC PULMONARY FIBROSIS AND EMPHYSEMA

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The association between idiopathic pulminary fibrosis (IPF) and emphysema was once believed to be improbable. That is until 2005, when after some previously descriptions of such cases and a proper study of the problem, Cottin first named it a specific syndrome: combined pulmonary fibrosis and emphysema (CPFE). We aimed to review current literature data regarding combined pulmonary fibrosis and emphysema. The syndrome appears mostly in male smokers and is characterized by exertional dyspnea, the association of lower-lobe fibrosis (usual interstitial pneumonia pattern) with upper-lobe emphysema (more frequent paraseptal), by preserved lung volumes that contrasts with severe alteration of gas transfer. Because of these peculiarities, a follow-up based on lung volumes is not desirable or useful. Diffusing capacity of lung for carbon monoxide could be used instead to determine the risk of complications (as pulmonary hypertension). Prognosis is more reserved than in IPF and emphysema alone, mostly because of the complications (severe pulmonary hypertension, which impacts significanty the survival, lung cancer and acute lung injury, studdied specifically in lung cancer patients with CPFE). CPFE consists of an association of specific imaging and lung function findings, manifested as severe dyspnea (mostly) in smoking male patients and has a high risk of complications.

Keywords: idiopathic pulmonary fibrosis, emphysema, pulmonary hypertension

IMMUNOMODULATORY THERAPY IN SARCOIDOSIS

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The purpose of this presentation is to summarize current treatment options and future directions for the development of new therapies in sarcoidosis, based on a review of current data regarding the immunomodulatory therapy in sarcoidosis. Sarcoidosis is a multisystem disease of unknown etiology characterized by tissue infiltration with noncaseating granulomas involving predominantly the lungs (90%) and intrathoracic lymph nodes. Spontaneous resolution of the disease is frequent, but progressive lung disease and disabling organ failure can occur in a significant number of patients. Although there are not standardized recommendations, corticosteroids are the mainstay of therapy. They are used for symptom relief, but their efficacy in the disease is unclear. Even more, there are studies that suggest that corticosteroid use may be associated with increased relapse rates. Considering the undesirable side effects of glucocorticoids and the existence of refractory cases, there is a widespread recognition that other therapeutic options need to be developed or adapted in sarcoidosis. Several alternative approaches have been proposed, such as the use of immunosuppressive, cytotoxic, and antimalarial drugs. Unfortunately, there are limited data regarding the indications and efficacy of these approaches in the management of pulmonary sarcoidosis. The treatment in sarcoidosis is still not totally standardized. New therapies are needed to enable the reduction or replacement of long-term therapy with glucocorticoids in patients with sarcoidosis

Keywords: sarcoidosis, corticosteroids, immunosuppressive drugs, immunomodulator therapy

THE UTILITY OF LUNG SONOGRAPHY IN THE ASSESSMENT OF IPF: FROM THEORY TO BEDSIDE

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Objectives. This study evaluated the value of sonographic B-lines ("comet tail artifacts"), which are long, vertical, well-defined, hyperechoic, dynamic lines originating from the pleural line, in assessment of idiopathic pulmonary fibrosis (IPF) and compared them with the findings of chest high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs). **Materials and methods.** High-resolution computed tomography (HRCT) is considered the gold standard for the diagnosis of IPF as it is a sensitive method to assess the extent and the pattern of pulmonary fibrosis. Reticular pattern involving the subpleural regions, bronchiectasis and honeycombing are HRCT signs of pulmonary fibrosis. Lung sonography, a non-invasive and non-radiation technique, is highly sensitive to variations of the pulmonary content and balance between air and fluids. Diffuse parenchymal lung diseases as pulmonary fibrosis is characterized by the presence of multiple diffuse bilateral B-lines. Twelve patients with IPF underwent transthoracic lung ultrasound for the assessment of the presence of B-lines and the distance between them. These findings were compared with that of chest HRCT (ground glass, reticular or honey combing) and PFT as forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity for carbon monoxide (DLCO). **Results**. All patients had diffuse bilateral B-lines. The distance between each of the two adjacent B lines correlated with the severity of the disease on chest HRCT where B3 (the distance was 3 mm) correlated with ground glass opacity and B7 (the distance was 7 mm) correlated with extensive fibrosis and honey combing. Also, the distance between B-lines inversely correlated with FVC, TLC and DLCO. **Conclusions.** B-lines that are lung ultrasound signs seem to be useful in the assessment of ILD.

Keywords: IPF, HRCT, lung sonography, B-lines, functional correlations

SMOKING-ASSOCIATED INTERSTITIAL LUNG DISEASES

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Cigarette smoking has diverse effects on the development of interstitial lung disease (ILD). Some ILDs are strongly associated with cigarette smoking including respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis (PLCH), and acute eosinophile pneumonia. Cigarette smoking increases the risk of developing idiopathic pulmonary fibrosis, rheumatoid arthritis-associated ILD, and pulmonary alveolar proteinosis (PAP). Sarcoidosis, hypersensitivity pneumonitis, and radiation-induced pneumonitis are all strikingly less prevalent in smokers than in non smokers, but a smoking protecting mechanism has yet to be identified. RB-ILD is histologically indistinguishable from respiratory bronchiolitis which is a very common incidental finding in cigarette smokers, also called "smoker's bronchiolitis", consisting of an accumulation of pigmented macrophages within respiratory bronchioles. Respiratory bronchiolitis can be considered as a sensitive histologic marker of cigarette smoking. High-resolution computed tomography (HRCT) may allow recognition and classification of the smoking-associated ILDs. HRCT appearances of RB-ILD frequently resemble those of subacute extrinsic allergic alveolitis. The history and BAL profile are usually definite in distinguishing between these disorders, biopsy is not needed. The clinical, radiologic, and histologic features frequently overlap, and mixed patterns of disease frequently may coexist in the same patient. The overlap is most significant between RB-ILD and DIP. Macrophages accumulation is bronchiolocentric in RB-ILD, producing centrilobular ground-glass opacity, and more diffuse in DIP, producing widespread ground-glass changes. The coexistence of upper lung nodules and cysts in a smoker allows the confident diagnosis of PLCH. Final diagnosis and identification of the specific entity can be achieved with certainty only after multi-disciplinary discussion. Smoking cessation should be a central part of therapy, while pharmacotherapy with corticosteroids or other immune modifying agents should be reserved for selected patients.

Keywords: interstitial lung diseases, smoking, RB-ILD, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis

INTERSTITIAL LUNG DISEASE IN RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is the most common autoimmune systemic inflammatory disease. Interstitial lung disease has been recognized as one of the most important co-morbidity in the course of this disease and a frequent extra-articular manifestation of RA. Pulmonary involvement in rheumatoid arthritis is heterogeneous regarding histopathological and radiographic appearance, but shows most common two ILD subtypes: usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). The risk of developing ILD is increased in male gender, higher age at RA onset, smoking, longstanding RA. Other risk factors were related to markers of disease severity and activity. High resolution CT (HRCT) scans are accurate in identifying ILD characteristic pattern and assessing disease severity, but in patients whom underlying pattern cannot be determined by imagistic studies, surgical biopsy should be considered. The importance of identifying patients with RA who are at risk for developing ILD becomes evident in the assessment of the significantly higher morbi-mortality for affected patients. Hence, all patients with RA should undergo annual screening for ILD and when ILD is suspected all patient should undergo PFTs and HRCT scans. The association between rheumatoid arthritis and interstitial lung disease is the most damaging, the effects ranging from subclinical inflammation to end-stage of pulmonary fibrosis.

Keywords: rheumatoid arthritis, interstitial lung disease, pulmonary fibrosis, usual interstitial pneumonia, nonspecific interstitial pneumonia

SCLERODERMA LUNG DISEASE

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Pulmonary disease in systemic sclerosis (SSc) mainly comprises interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), which together account for 60% of SSc-related deaths. Early death from SSc-ILD is relatively uncommon with an estimated survival of 85% at 5 years. The presence of PAH in SSc has a major negative impact on survival; it is the second most frequent cause of death behind ILD, causing 28% of all deaths. Indirect pulmonary complications in SSc comprise gastro-oesophageal reflux and aspiration, infection, drug toxicity, malignancy and respiratory muscle weakness. The treatment should be individualized and made on the basis of the clinical significance of the disease and the likelihood of future progression. Key findings relevant to the management of patients with SSc-ILD are: the risk of progression of SSc-ILD is highest in the first four years of the disease, especially in the first two years, and in a small subset of patients with lung disease that precedes the cutaneous manifestations of SSc; it is generally accepted that treatment should be introduced if there is evidence of an ongoing progression based on pulmonary function decline or radiographic deterioration; more severe pulmonary functional impairment at presentation is indicative of higher risk of mortality. Nonselective immunosuppressors are the main treatment for ILD. The most widespread treatment regimen is low dose corticosteroid therapy in combination with an immunosuppressive agent, most commonly oral cyclophosphamide. Intravenous cyclophosphamide has been increasingly used, with evidence of partial regression of lung disease. Novel therapies towards specific molecular and cellular targets have been suggested, in particular rituximab has shown promising results.

Keywords: scleroderma, interstitial lung disease, pulmonary hypertension, immunosuppressive treatment

MANAGEMENT AND PROGNOSTIC FACTORS OF ANTINEUTROPHIL CYTOPLASM ANTIBODY (ANCA)-ASSOCIATED VASCULITIS

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The antineutrophil cytoplasm antibodies (ANCA)-associated vasculitis are a group of rare but unpredictable and potentially life-threatening conditions. These systemic and autoimmune diseases are characterized by necrotizing small vessel vasculitis and the association with ANCA. ANCA-associated vasculitis includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The diagnosis of these patients is challenging due to the heterogeneity of clinical features and an unpredictable evolution from slow progression to acute renal failure or pulmonary hemorrhage. For a definitive diagnosis in a suspected patient, a biopsy should be performed. The treatment requires potent immunosuppression with a dramatical improvement of the overall survival, but with frequent treatment-related side effects. Recent progress in experts recommendations is made about the evaluation of these patients in centers of expertise, about refining the amount of treatment immunosuppression following quantification of disease activity, the management of relapses and the importance of comorbidity assessment. These recommendations further improve patient's outcome. The prognosis differs for distinctive diseases, with a higher risk for relapses for GPA patients but in MPA with a significantly much larger number of patients on hemodialysis. **Conclusions**. This presentation will focus on therapeutic options and the prognostic factors of different ANCA-associated vasculitis.

Keywords: antineutrophil cytoplasm antibody, vasculitis, pulmonary

SURGICAL AND ANESTHESIOLOGICAL ASPECTS REGARDING PULMONARY BIOPSY IN ILD PATIENTS

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Introduction. Interstitial lung disease (ILD) and Pulmonary Fibrosis are general terms used to describe inflammatory and fibrotic disorders of lung tissue (interstitium). There are over 100 known causes of interstitial lung disease and pulmonary fibrosis. In this paper, we discuss the main surgical and anesthesiological aspects regarding pulmonary biopsy in ILD patients. The main goals in anesthesia management in ILD patients include: preoperative optimization (limited), minimally invasive (local anesthetic or regional) or maximum support (slow wean) and lung protective ventilation. Regarding the surgical techniques in ILD patients, traditionally, the diagnostic procedure of choice was the open-lung biopsy, with a positive diagnosis rate of more than 90%. Before the advent of VATS, the morbidity and pain of a thoracotomy often deterred clinicians from performing lung biopsies until late in the course of the disease. Lung transplantation is introduced, but as a very expensive intervention. VATS patients enjoyed a lower complication rate than open-lung biopsy ILD patients (2 of 22 versus 4 of 21), shorter mean duration of chest drainage (1.4 days versus 3.2 days), and shorter hospital stay (2.6 days versus 5.7 days). Survival rate after unilateral transplantation: 74% at one year; 58% at 3 years; 47% at 5 years; 24% at 10 years. The survival rate in bilateral transplantation is lower than in the unilateral one. A proper selection of cases and of surgical technique is mandatory. Individualised anesthesia procedure is recommended, and the experienced team must always be prepared for the worst postoperative course. Minimum two sites of biopsy are mandatory for a proper diagnosis. The lung transplantation is the only intervention that increases survival in idiopathic pulmonary fibrosis, but it is not supported by the Romanian insurance companies.

Keywords: interstitial lung diseases, lung biopsy, video-assisted thoracic surgery, anesthesia

INTERSTITIAL LUNG DISEASES AND MYCOBACTERIAL DISEASES: PERCEPTIONS AND NEEDS

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There is a large group of about 200 different diseases included in the large family of diffuse interstitial parenchymal lung diseases (IPD), with similar clinical, imaging, or pathologic manifestations. They are increasingly common conditions which pose many diagnostic and therapeutic challenges, leading to misdiagnosis and mismanagement. The histopathological pattern is mandatory for differentiation. Mycobacterial diseases, mainly pulmonary tuberculosis, are a relatively common cause of chronic lung infections worldwide and the diagnosis and treatment represent very important clinical issues. Pulmonary tuberculosis demonstrates a variety of clinical and radiological features and the diagnosis is challenging in people with suspected tuberculosis with unusual radiographic findings and repeated negative sputum smears. On most occasions treatment of pulmonary tuberculosis is started by physicians based predominantly on radiological opacities. Early diagnosis is equally significant as treatment in the reduction of morbidity and mortality associated with pulmonary tuberculosis. In this presentation, we analyze the processes of organization and fibrosing in the tuberculosis-involved and non-tuberculosis of the lungs, radiological patterns, clinical, functional and prognostic features that can differentiate between the two, in both imunocompetent and imunodeprimant patients.

Keywords: interstitial lung diseases, fibrosis, *Mycobacterium spp.*, pulmonary tuberculosis

CHILD LUNG INTERSTITIAL DISEASE

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The involvement of pulmonary interstitium in children represents a real challenge for the respirologists. Pulmonary interstitial diseases are extremely heterogeneous, with multiple phenotypes and genotypes, having a very low prevalence among the 0-14 year-old population, mainly in children under 2 years of age. The aim consists in presenting the actual data of this orphan group of diseases and disorders. In order to assess the natural course, phenotypic and genotypic variability, the involvement of interstitial lung disease in children (chILD), and effectiveness of treatments, we performed a meta-analysis of literature data, guidelines, reviews and case reports. An update of diffuse lung disease and child syndrome, inclusive asymptomatic forms of chILD, was performed based on Classification of European Respiratory Task Force, Official American Thoracic Society Guideline of Classification, Evaluation and Management of Childhood Interstitial Lung Disease in Infancy, as well as the Action CA16125 of European network for translational research in children and adult interstitial lung disease. Because of the varied and extremely heterogeneous chILD expression, there are a few and inconclusive data about diagnosis, disease progression and therapy management strategies. Further multidisciplinary research for early accurate diagnosis and personalised management of chILD are needed.

Keywords: interstitial lung disease, children, chILD, meta-analysis

INTERSTITIAL LUNG DISEASE – IS BIOPSY ALWAYS NECESSARY?

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Background. Interstitial lung diseases (ILD) are conditions with a low incidence, nonspecific clinical presentation, various imaging findings and different outcome, depending on the disease's subtype and the time to a definite diagnosis and optimal therapy institution. **Clinical case.** We present the case of a 58-year-old male, ex-smoker (15 packs-years, he had stopped smoking 20 years ago), with no professional or domestic exposure to airborne particles or antigens, who was admitted into our clinic for exercise dyspnea, unproductive cough and night sweats, which started 3 weeks before presentation and had a progressive evolution. He previously had a similar episode (5 years earlier), which responded to a short course of antibiotics. The initial evaluation identified bilateral basal crackles at the clinical exam, oxygen desaturation on exercise, multiple alveolar opacities at the chest X-ray and restrictive syndrome on spirometry. In order to establish the diagnosis, we performed a high resolution CT scan, bronchoscopy with bronchioloalveolar lavage and lung biopsy. The histopathological exam of the lung biopsy was extremely helpful, as the patient had a difficult evolution with systemic cortisone therapy. **Conclusions.** Interstitial lung diseases have pleomorphic imaging aspects that require an extensive differential diagnostic. Even if not always mandatory, lung biopsy should be obtained whenever possible, as it is very important for guiding therapy, especially when the patient's clinical course is not favorable with a given treatment.

Keywords: interstitial lung disease, high resolution CT scan, lung biopsy

INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES (IPAF) – A NEW ENTITY?

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Interstitial lung diseases (ILD) can be one of the features of some collagen tissue diaseases (CTD), or occult CTDs may have an onset mimicking an ILD. Some patients with ILDs may have some subtle features suggesting an underlying immune process, without fulfilling the criteria for a specific CTD. Several terms and criteria were proposed: unclassifiable CTD related ILD (UCTD-ILD), lung dominant CTD, autoimmune featured ILD. Since 2013, European Respiratory Society and American Thoracic Society designed the "Task Force on Undifferentiated Forms of CTD-ILD", including an international panel of experts, aiming to define the nomenclature and features of a cohort, as a base for further research. The result was a consensus statement, published in 2016, defining the name as Interstitial Pneumonia with Autoimmune Features. Patients need to fulfill simultaneously four elements: 1. ILD; 2. Exclusion of alternative etiologies; 3. Does not match criteria for a CTD; 4. At least one feature of two domains: clinical, serologic, morphologic. UIP pattern is not an exclusion criterion, but, if present, patients need to fulfill two others. Subsequent observational studies described a percentage of IPAF in 7.3% to 14.07% of ILD patients, some described a female and NSIP pattern predominance, while others equal gender distribution and almost 50% UIP patterns. Some studies suggested better survival than IPF, while another study suggested the survival is impaired if UIP pattern is present. The diagnosis needs a multidisciplinary approach (pulmonologist and rheumatologist). Still, there are unanswered questions: is this a true disease or just a research-based cohort? What should the therapeutic approach be? Is IPAF a provisional diagnosis before the full onset of a CTD? Further research for better defining IPAF cohort is needed.

RESULTS OF TREATMENT WITH SIROLIMUS IN LYMPHANGIOLEIOMYOMATOSIS

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Introduction. Lymphangioleiomyomatosis (LAM) is a rare, progressive lung disease that primarily affects women of childbearing age. The disease is characterized by abnormal proliferation of smooth muscle cells invading the airways and blood/lymph vessels, leading to airflow and vascular obstruction, lung destruction and progression to respiratory failure. It affects the lungs, kidneys and lymphatic system. Sirolimus (Rapamune) is an immunosuppressive drug (mTOR inhibitor) which was originally indicated for the prophylaxis of organ rejection in renal transplant patients. Sirolimus subsequently got the FDA approval for treatment of patients with LAM. The indication was based on results of MILES trial (International Multicenter Efficacy of Sirolimus), which evaluated the effects of Rapamune in 89 patients with LAM with moderate functional impairment; stabilization of lung function (FEV1) after one year of treatment was demonstrated. **Materials and methods.** The results of treatment with sirolimus in two cases of LAM diagnosed and followed in the "Marius Nasta" Institute are presented. **Results.** Although disease severity at the begining of therapy was higher than in the MILES study, the results are similar to those reported in literature – favorable effect on FEV decline compared to the tracking before starting treatment or slowing the lymph accumulation in the pleural space. There were no major side effects. **Conclusions.** Sirolimus is reimbursed in Romania only for kidney transplant patients, so the problem of high costs of treatment would be a major limitation for most patients with LAM. Authorization procedures for using sirolimus as a treatment of last resort in LAM, on humanitarian grounds, are ready to be finalised.

Keywords: lymphangioleiomyomatosis (LAM), sirolimus, FEV1, lymphangioleiomiomatosis

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Pumonary alveolar proteinosis (PAP) is a rare pulmonary disease with poorly defined etiology, characterized by the accumulation of abnormal surfactant, lipoproteinaceous material containing positive PAS corpuscles. All studies show an incidence and prevalence of less than 0.5-1/100.000 inhabitants, and in Romania it is certainly underdiagnosed. There are three forms of PAP – congenital, secondary and acquired –, the latter form representing over 90% of cases. The presence in the bronchoalveolar lavage fluid and in the serum of acquired PA patients of granulocyte-macrophage colony stimulating factor (GM-CSF) autoantibodies and the discovery of a latex-agglutination test, with a specificity of 98% and a sensitivity of 100% for PAP acquired form, opened a new perspective on acquired pathogenesis and PAP therapy. Subcutaneous administration of GM-CSF is promising, at least in some cases, but not sufficiently conclusive, so that Whole Lung Lavage (WLL) remains the golden standard of therapy. WLL indications are: a positive PAP diagnosis, a shunt fraction greater than 10%, and effort dyspneea with hypoxemia. The procedure is performed under general anesthesia, a hypno-relaxing technique, with a double lumen tube intubation and separate ventilation of the two lungs. Minimal monitoring includes pulse oximetry, continuous ECG, TA, capnography, diuresis and a blood line for blood gases. One lung is ventilated and the other is washed in 0.5-1 L sequences until the liquid rinses. More than 25 liters are sometimes required. The procedure is repeated on the other lung usually after at least 3 weeks. In exceptional cases, in children or in adults with severe hypoxemic forms, it is possible to practice WLL with extracorporeal circulation which allows bilateral lavage and recovery by mechanical ventilation. The first WLL under general anesthesia was performed in the Anesthesiology and ICU Department of the "Marius Nasta" Institute, in Bucharest, in 2000. Since then, the technique has become a routine, with a history of over 150 LPT, having one of the highest statistics for a single center. Following WLL, there is a significant improvement in oxygenation, respiratory function and improved survival. At 5 years, survival was on average 94% for those with LPT compared to an average of 85% for those without WLL.

Keywords: Whole Lung Lavage, pulmonary alveolar proteinosis

IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS – A RARE ENTITY OF INTERSTITIAL LUNG DISEASE

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Pleuroparenchymal fibroelastosis (PPFE) is a rare disease characterized by pleural and subpleural parenchymal fibrosis and elastosis, with an upper lobe predilection. Although PPFE has been reported in association with other different conditions, there are cases described as idiopathic (IPPFE), and included as a distinct clinico-pathologic entity in the latest international multidisciplinary classification of the idiopathic interstitial pneumonias. The aim of this lecture is to summarize the current evidence on IPPFE, in terms of clinical, radiologic and pathologic features, natural history and potential treatments. We reviewed the latest published data from the literature, including case reports, reviews, prospective and retrospective studies. PPFE shares some clinical features with other chronic interstitial pneumonias (dyspnea, dry cough), and is radiologically characterized by upper lobe pleural thickening and subpleural parenchymal fibrosis, with lower lobe involvement less marked or absent. The main histological findings include upper zone fibrosis of the visceral pleura, subpleural intra-alveolar fibrosis with elastosis. The prognosis is highly variable and largely unpredictable. Pneumothorax is a common complication and may occur at presentation or at other times during the course of the disease. The pathogenesis of PPFE remains unclear, although it is proposed that the starting point may involve an element of acute lung injury or interstitial inflammation. No treatment has yet been shown to modify the natural course of disease, and lung transplantation remains the only curative option. Recognizing the specific features of PPFE is essential to establish early diagnosis strategies, and to implement appropiate management by the multidisciplinary team.

Keywords: pleuroparenchymal fibroelastosis, rare interstitial lung disease, fibrosis

NOT EVERY PROGRESSIVE EVOLUTION IS IPF...

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Introduction. The differentiation between idiopathic pulmonary fibrosis and other interstitial diseases is difficult when these have a chronic progressive evolution to lung fibrosis. We present the case of a 56-year-old female patient, former smoker, obese, presenting with moderate exercise dyspnea, dry cough and joint pain, symptoms presented for 7 years. She was previously diagnosed with an interstitial lung disease and treated with oral corticosteroids for 18 months, with modest improvement. Lung function tests showed moderate restriction and decreased alveolar diffusion. HRCT showed lung volume loss, very little ground glass opacification, linear opacities and traction bronchectasis in all segments, with a subpleural predominance, with no honeycombing. The six-minute walk test showed a decrease in oxygen saturation from 96% to 75%. Surgical lung biopsy revealed a chronic hypersensitivity pneumonia. The history revealed the presence of two birds in the house, that were exiled. The patient received oral corticosteroids with associated cyclophosphamide in pulse therapy, later replaced by azathioprine. Long-term functional follow-up showed a slow but constant decline in vital capacity and diffusion capacity over the past 4 years, that continues after the eviction of the birds and despite immunosuppresive therapy. **Discussion.** The diagnosis of chronic hypersensitivity pneumonitis was enforced both by proven exposure to birds and lung biopsy, but HRCT pattern is possible UIP, while the long-term evolution mimicks idiopathic pulmonary fibrosis. Discussion can be made on the true identification of the incriminated allergen, and on the value of surgical lung biopsy in the final diagnosis.

Keywords: chronic hypersensitivity pneumonitis, lung fibrosis, lung function tests, progressive evolution, lung biopsy