sciendo Internal Medicine 2024 vol. XXI No. 2 - www.srmi.ro 111
10.2478/inmed-2024-0293

PERSPECTIVES IN SMOKING RELATED INTERSTITIAL LUNG DISEASES

Ancuța Constantin[1,2], Maria-Beatrice Catrangiu[1], Ana-Luiza Iorga[1,2]
[1]Institute of Pneumology "Marius Nasta", Bucharest, România
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, România
Corresponding author: Maria-Beatrice Catrangiu
E-mail: maria-beatrice.catrangiu@rez.umfcd.ro

Abstract
Interstitial lung disease is a generic term encompassing a wide range of unrelated conditions that have in common a tendency to cause shortness of breath and/or cough associated with bilateral abnormal opacity of various types on conventional chest X-rays or high-resolution computed tomography scans, symptoms including dyspnea, wheezing, cough, and/or sputum production. This study aimed to show that cigarette smoke is a powerful inducer of inflammation and the cause-effect relationship between cigarette smoking and interstitial diseases – respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP). We bring to your attention the cases of two patients, heavy smokers with HRCT images suggestive for RB-ILD and DIP. The patients present to the on-call room with dry cough, exertional dyspnea and receive corticosteroid treatment with the recommendation to cease smoking. An approach would be to target high-risk populations, such as older adults with a history of smoking for early diagnosis of parenchymal lung diseases (e.g. ILD and chronic obstructive pulmonary disease) or lung cancer.
Keywords: *smoking, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, corticosteroid therapy.*

Rezumat
Boala pulmonară interstițială este un termen generic care cuprinde o gamă largă de afecțiuni neînrudite care au în comun tendința de a provoca dificultăți de respirație și/sau tuse asociată cu opacitate anormală bilaterală de diferite tipuri la radiografiile toracice convenționale sau tomografiile computerizate de înaltă rezoluție, simptome cum sunt dispnea, respirația șuierătoare, tusea și/sau producția de spută. Această lucrare și-a propus să arate că fumul de țigară este un inductor puternic al inflamației și să evidențieze relația cauză-efect dintre fumatul de țigară și bolile interstițiale - boala pulmonară interstițială asociată cu bronșiolita respiratorie (RB-ILD) și pneumonia interstițială descuamativă (DIP). Vă aducem la cunoștință cazurile a doi pacienți, mari fumători cu imagini HRCT sugestive pentru RB-ILD și DIP.



Internal Medicine

Clinical Cases

Pacienții se prezintă la camera de gardă cu tuse uscată, dispnee de efort și primesc tratament cu corticosteroizi, cu recomandarea renunțării la fumat. O abordare ar fi vizarea populațiilor cu risc ridicat, cum ar fi adulții în vârstă cu antecedente de fumat, pentru diagnosticarea precoce a bolilor pulmonare parenchimatoase (de exemplu, ILD și boala pulmonară obstructivă cronică) sau cancerul pulmonar.

Cuvinte cheie: fumat, boală pulmonară interstițială asociată bronșiolitei respiratorii, pneumonie interstițială descuamativă, terapie cu corticosteroizi.

Cuvinte cheie: *fumat, boală pulmonară interstițială asociată cu bronșiolita respiratorie, pneumonie interstițială descuamativă, terapie cu corticosteroizi.*

Interstitial lung disease is a generic term encompassing a wide range of unrelated conditions that have in common a tendency to cause shortness of breath and/or cough associated with bilateral abnormal opacity of various types on conventional chest X-rays or high-resolution computed tomography (HRCT) scans. Interstitial lung diseases consist of conditions of known causes (rheumatic, environmental or drug-related diseases) as well as conditions of idiopathic cause[1]. Causes can vary from hypersensitivity pneumonitis, medication - induced pneumonitis, occupation-related, autoimmune-related and other forms of interstitial lung disease including Lymphangioleiomyomatosis (LAM), Pulmonary Langerhans cell histiocytosis (PLCH), and eosinophilic pneumonia.

Interstitial pneumonias are further classified as chronic fibrosing (IPF – Idiopathic pulmonary fibrosis, NSIP – Nonspecific interstitial pneumonia), acute or subacute fibrosing (COP - Cryptogenic organizing pneumonia, AIP - Acute interstitial pneumonia), or smoking-related. Lymphoid interstitial pneumonia is usually associated with other pathological processes such as rheumatic disease or immuno-suppression[1].

The category of smoking-related idiopathic interstitial pneumonias (IIPs) includes most cases of desquamative interstitial pneumonia (DIP) and nearly all cases of respiratory bronchiolitis - associated interstitial lung disease (RB-ILD) and Langerhans' cell histiocytosis. DIP and RB-ILD share several overlapping clinicopathologic features, and both have a better prognosis than usual interstitial pneumonia (UIP)[1].

Cigarette smoke is a powerful inducer of inflammation, which results primarily through

an increased number of macrophages that are attracted and retained in the lungs. These macrophages attract additional inflammatory cells to the lungs, including neutrophils, monocytes, eosinophils and T lymphocytes. The result is a destructive cascade of elastolytic compounds and reactive oxidative species that destroy the structure of the lung, leading to emphysema and obstructive bronchiolitis. Closely related to this destructive inflammatory cascade is a distorted attempt to repair the lungs and airways, which can be seen under the microscope as collagen and fibrous tissue deposits. This form of fibrosis is associated with the intensity and duration of exposure to cigarette smoke[2].Also, the nicotine inhaled from cigarette smoke also has pleiotropic effects that appear to be concentration-dependent. It has been hypothesized to enhance fibrogenesis through several mechanisms, including endothelial and epithelial damage, production of proinflammatory cytokines, and activation of transforming growth factor (TGF)-β, macrophages and fibroblasts[2].

It has been proven that osteopontin (OPN), a glycoprotein with cytokine properties, has significantly increased in patients with smoking-related ILDs[3]. This glycoprotein is found in the extracellular matrix of bone and has chemotactic properties for macrophages, monocytes, dendritic cells and Langerhans cells. Interestingly, this study demonstrated evidence of chronic nicotine stimulation in macrophages of patients with smoking-related ILPs[2].

Air pollution may be associated with the development, progression or exacerbation of ILD through mechanisms of lung injury, alveolar injury, telomere shortening, cellular senescence, changes in the respiratory microbiome, inflammation and/or abnormal lung repair[4]. In addition, individual genetic or epigenetic factors may affect the phenotypic expression of ILD resulting from environmental exposures, and future research is needed to outline these mechanisms[5].

RB-ILD: Respiratory bronchiolitis is a well-recognized pathologic lesion found in the lungs of cigarette smokers that is generally not associated with respiratory symptoms.

RB-ILD is a frequent pathologic finding in current or previous smokers (in up to 90% of patients), no gender predilection, 30-60 years old, it is defined by the presence of changes of RB as the sole pathologic finding clinical evidence of ILD. The degree to which fibrosis extends into the alveolar wall has sometimes been used to distinguish RB from RB-ILD[6]. The key histopathologic features of RB are the presence of tan-pigmented macrophages (Figure 1) (also known as smokers' macrophages) in the respiratory bronchioles, a patchy submucosal and peribronchiolar infiltrate of lymphocytes and histiocytes, and peribronchiolar fibrosis that extends into contiguous alveolar walls[6].

Clinical presentation of patients with RB-ILD typically occurs with subacute symptoms of dyspnea, wheezing, cough, and/or sputum production.

Less common initial manifestations could be pneumothorax, hemoptysis, and acute respiratory failure and about 40-70% of patients have fine, bibasilar end-inspiratory crackles on chest examination[7].The crackles are described as being more rough sounding than those heard in other ILDs, such as idiopathic pulmonary fibrosis. They occur throughout inhalation and sometimes continue into expiration. Clubbing of the digits is unusual but has been reported in a small number of patients with RB-ILD.

The most common pulmonary function test finding in RB-ILD is a mixed obstructive-restrictive pattern with mild to moderate



reduction in diffusing capacity for carbon monoxide (DLCO). The mixture of obstructive and restrictive patterns is attributed to the airway inflammation from heavy cigarette smoke exposure, which causes obstructive physiology, and the interstitial disease associated with RB-ILD, which causes restriction and a gas transfer abnormality. Occasionally, an isolated increase in residual volume is also noted[7].

High-resolution computer tomography (HRCT) findings are nonspecific and include diffuse or patchy ground-glass opacities, centrilobular nodules, and air trapping. HRCT findings included central bronchial wall thic kening (90%), peripheral bronchial wall thickening (86%), centrilobular nodules (71%), and ground-glass opacity (67%)[8]. Ill-defined centrilobular nodules with upper lung zone predominance and without tree-in-bud opacities were noted in patients with RB-ILD. Atelectasis, intralobular lines, interlobular septal thickening, and peripheral blebs have been reported less commonly[9].

The differential diagnosis of RB-ILD includes a number of bronchiolar disorders and diffuse parenchymal lung diseases, such as nonspecific interstitial pneumonia, idiopathic pulmonary fibrosis (IPF), DIP, pulmonary Langerhans cell histiocytosis, hypersensitivity pneumonitis, and diffuse alveolar hemorrhage[8]. Hypersensitivity pneumonitis may present with clinical features resembling those of RB-ILD, such as centrilobular ground-glass nodules observed on HRCT. However, the histopathology of hypersensitivity pneumonitis is characterized by poorly formed, noncase-ating granulomas or a prolific mononuclear cell infiltrate, neither of which are seen in RB-ILD.

Lymphocytic predominance on bronchoal-veolar lavage in a patient with centrilobular nodules and subtle ground-glass nodules should prompt consideration of hypersen-sitivity pneumonitis over RB-ILD[9].

Smoking cessation is the most important recommendation for a patient with RB-ILD. However, clinical and physiological improvement following smoking cessation is delayed and often incomplete. Data from case reports and small case series suggest that approximately two-thirds of those who quit smoking have clinical improvement[10]. Long-term survival is common among patients with RB-ILD, 75% of the patients lived longer than 7 years after being diagnosed. Several small case series suggest that RB-ILD has a good prognosis and is often reversible with smoking cessation[10]. For patients who have progressive RB-ILD despite smoking cessation, glucocorticoid therapy is initiated. When initiating oral glucocorticoid therapy is started with prednisone at 0.5 mg/kg ideal body weight per day up to a maximum of 30 mg/day for one month followed by 20 mg/day for an additional two months[11].

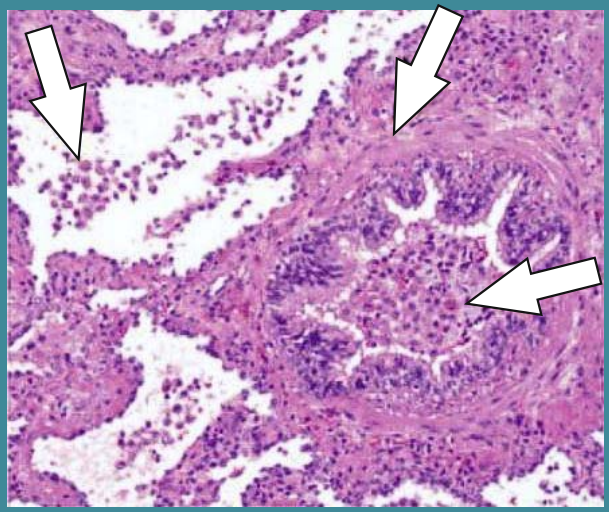


Figure 1. *Photomicrograph (original magnification, x100; hematoxylin-eosin stain) showing the characteristic histologic features of RB-ILD. Pigmented macrophages in a terminal bronchiole and the adjacent alveoli (arrows), and moderate peribronchiolar inflammation and fibrosis (arrowhead) are present.*

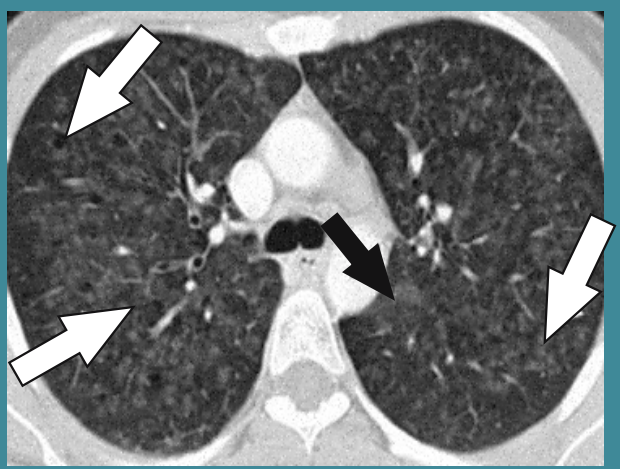


Figure 2. *Respiratory Bronchiolitis - Associated Interstitial Lung Disease: Radiologic Features with Clinical and Pathologic Correlation Jai Soung Park, Kevin K. Brown, Rubin M. Tuder, Valerie A. E. Hale, Talmadge E. King, Jr., and David A. Lynch*

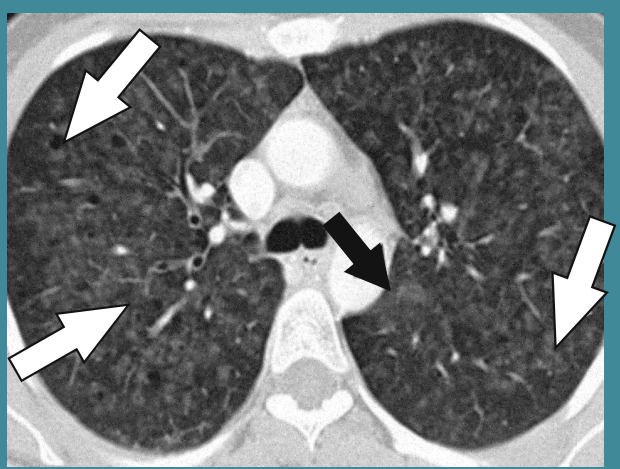




Figure 3. *RB-ILD in a 44-year-old woman with a 20 pack-year smoking history. HRCT image of the upper lung lobes shows centrilobular nodules (white arrows), patchy ground-glass opacities (black arrow), and mild coexisting centrilobular emphysema (arrowhead). *Mueller-Mang C, Grosse C, Schmid K, et al.: What every radiologist should know about idiopathic interstitial pneumonias. Radiographics 2007, 27:595-615. With permission from The Radiological Society of North America.*



When a patient responds or stabilizes with treatment, the prednisone dose is gradually tapered, aiming to reach 5 to 10 mg daily or on alternate days, by the end of six to nine months, with attempted cessation after approximately 12 months. Even among patients with an initial response, worsening during tapering or discontinuing glucocorticoids is not uncommon. When no apparent improvement is noted after the first three months of treatment, glucocorticoids therapy should be discontinued as quickly as possible and a surgical lung biopsy should be considered for diagnostic clarification[12].

Case presentation

We present the case of a 43-year-old woman, a 24 packs-year smoker, with occupational exposure to respiratory hazards: strong disinfectants and detergents for 5 years. We mention that the patient lives in an urban environment and her hobby is walking in the park. She was brought to the hospital following the appearance of non-specific symptoms for 4 months. We note expiratory dyspnea and dry cough. Chest X-ray shows interstitial lesions and a native chest CT scan is performed. On the clinical exam, the patient is pulmonary normal, with an oxygen saturation of 96% in ambiental air, tachycardia 112 bpm, BP 130/80 mmHG, and a BMI of 20,3 kg/m2. On the HRCT we can see mosaic attenuation and thickening of interlobular septs (Figure 4). The investigations show normal lung function test values, including DLCO value (81,9 %). Bronchoscopy revelead minimal mucosal edema and the cytological result of BAL were characteristic to smokers (alveolitis with 38 million cells; Ma= 95,2%). The 6 minutes walking test has shown no desaturation and the patient walked the full distance. The next step was to refer the patient to the thoracic surgery clinic for lung biopsy.

Following the biopsy, the histopathological aspect is suggestive for RB-ILD pattern. Bronchioles have slightly thickened walls, due to minimal fibrosis, and contain yellow-brown pigmented macrophages, showing a respiratory bronchiolitis aspect. The peribronchiolar parenchyma and also the periphery of the lobe in some cases is characterized by the accumulation of endoalveolar pigmented macrophages. Associated, there are also areas of emphysema, minimal focal fibrosis. A 6 months monitoring period was recommended, with mandatory smoking cessation quest, and adviced to avoid exposure to environmental toxic noxes. But the patient delayed the follow-up period with another 6 months and the thoracic CT was done after 12 months (Figure 6). After this period the patient has had no symptoms to declare, and the respiratory

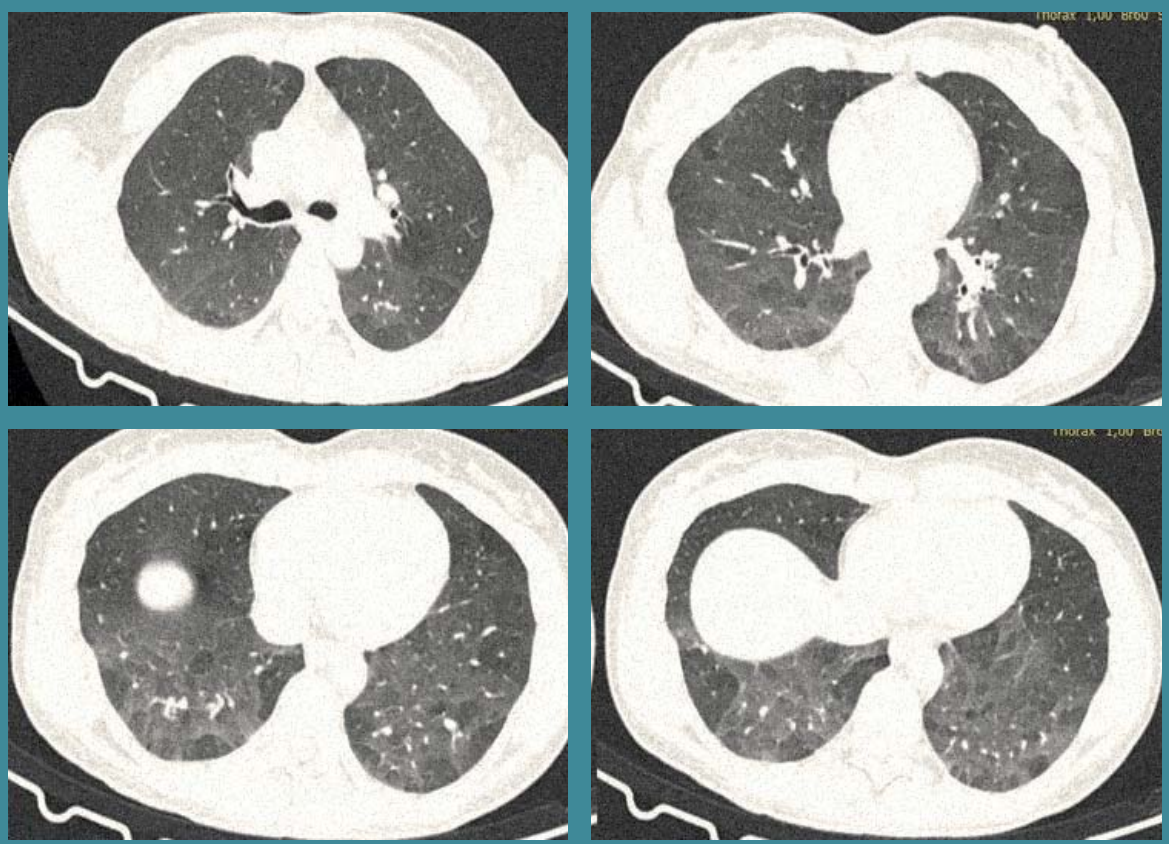


Figure 4. *Patient's thoracic CT scan*

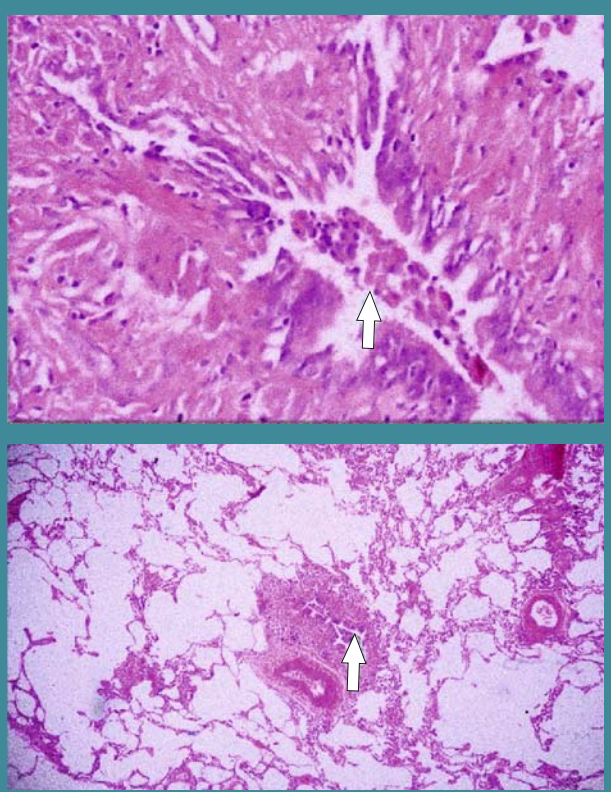


Figure 5. *Microscopic image - lung biopsy by Dr Magheran Elena - Anatomopathologist at M. Nasta Institute, Bucharest. Up - LIL fragment: discreetly diminished elasticity, vaguely nodular aspect.*

Down - LUL fragment: pulmonary parenchyme fragments with superposable histopathological aspects for centrolobular damage



Characteristics	RB/RB-I LD	DIP
Incidence according to sex	M = F	M > F
Clinical features	Chronic cough	Chronic cough with bilateral crackles
	Inspiratory crackles	Digital clubbing (-50%)
PFTs	Normal or mixed restrictive-obstructive pattern	Restrictive pattern
	Decreased Dlco	Reduction in Dlco
Bronchoalveolar lavage	Increased macrophages	Increased macrophages
	Modest increase in neutrophils	Mild increase in the percentage of eosinophil and neutrophil cells
Key histopathological finding	Pigmented macrophages in the respiratory bronchioles	Diffuse and uniform, filled with pigmented macrophages
Radiological findings	Centrilobular nodules and GGOs, predominantly in the upper and middle lobes	Diffuse GG0s, predominantly lower and subpleural
	Mild interlobular septal thickening	
Spontaneous improvement	Possible	Occasionally
Treatment	Smoking cessation	Smoking cessation and steroid

***Table 1**. Summary of key features. Abbreviations: DIP, desquamative interstitial pneumonia; DLco, diffusing capacity of the lung for carbon monoxide: F. female; GGO, ground-glass opacity: ILEX interstitial lung disease: M, male; PFT, pulmonary function test; RB, respiratory bronchiolitis.*

functional test were normal, including the DLCO.

Desquamative interstitial pneumonia is characterized by the presence of pigmented macrophages diffusely distributed in the alveolar spaces. Although the alveolar walls are variably thickened by diffuse fibrosis and mild infiltrates of chronic inflammatory cells, the alveolar wall architecture is preserved and usually lacks alveolation.[13] Histologically, the findings in DIP overlap with those in RB-ILD, and separation of the two is based on the distribution of pigmented macrophages. In DIP, macrophages are diffusely distributed throughout the secondary lobe, whereas in RB-ILD they are bronchiolocentric. However, macrophage distribution can vary considerably from alveolus to alveolus and from histological section to histological section, making the separation of DIP from RB-ILD difficult and often quite arbitrary.

Assessment of macrophage distribution may be limited by sample size and biopsy site. Disease appearance has a strong association



Figure 6. *First thoracic CT scan vs. second thoracic CT scan after a period of 12 months*

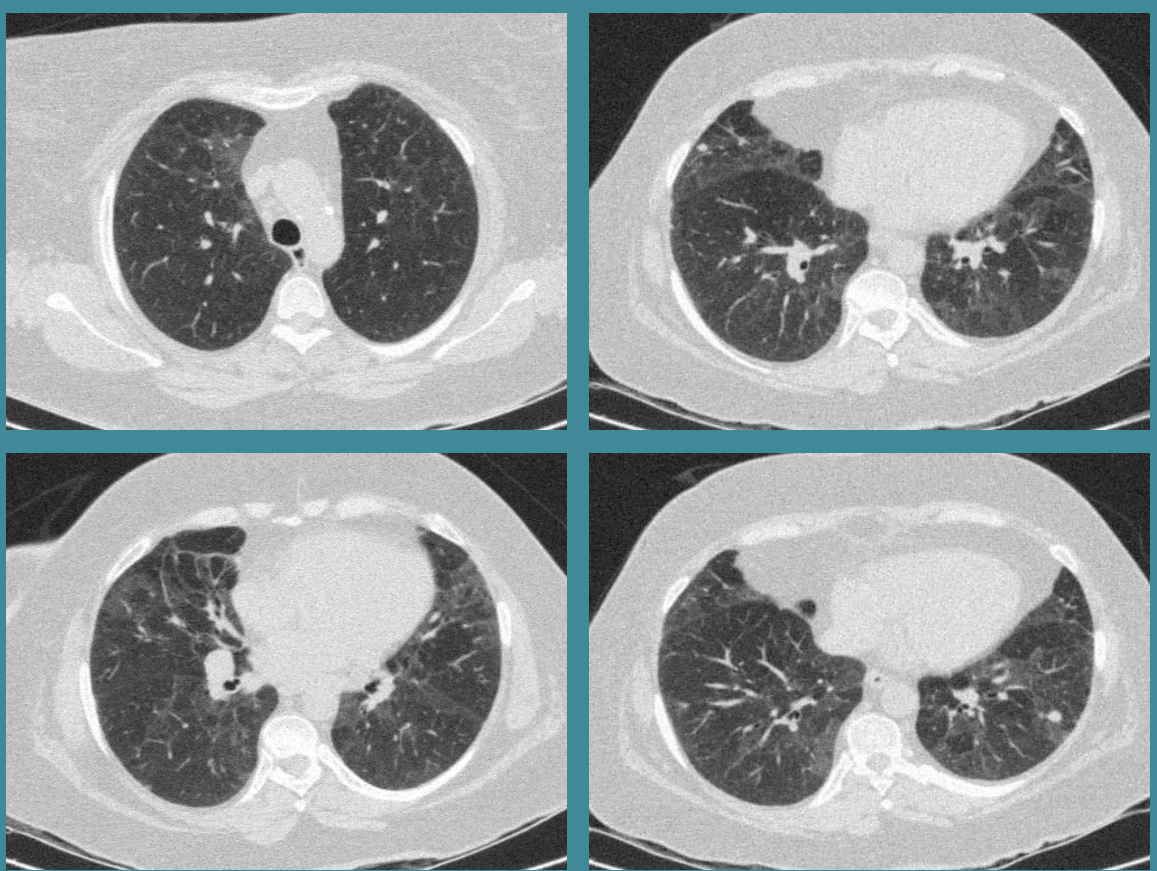


Figure 7. *Chest High Resolution Computed Tomography*

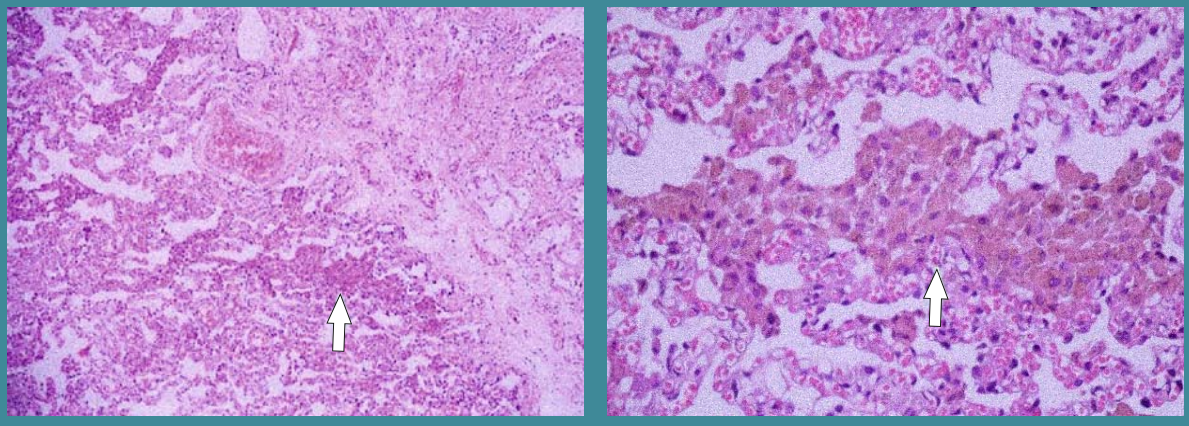
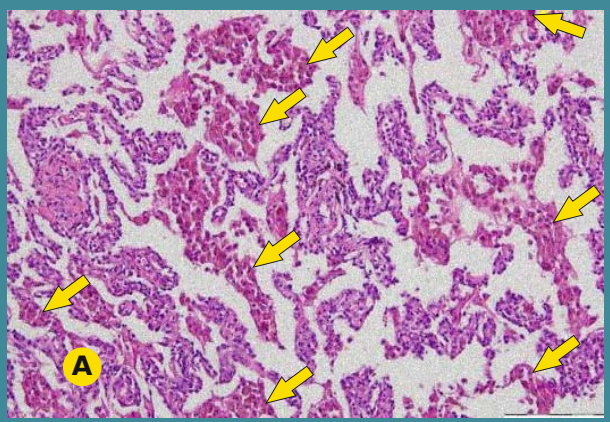


Figure 8. *Pulmonary biopsy- DIP vs RB-ILD Credits by Dr Adrian Tudor Anatomopathologist, "M. Nasta" Institute*

with current and previous smokers. Between 60% and 90% of PID cases are reported in smokers, but other risk factors such as external noxious substances, autoimmune diseases, infections or medications are also reported[13]. Radiological findings in DIP, on HRCT, are homogeneous or patchy increase in lung attenuation or ground glass, which is reported as the most common finding in DIP patients in most series. The middle and lower lung areas are predominantly involved and there is a predilection for lung peripheral involvement. Long-term radiographic follow-up demonstrates a radiographic progression with alveolar development in about 10% to 20% of patients[14].

Smoking cessation is considered an essential component in the management of DIP in smokers, although the exact impact is unclear. Some patients have improved with smoking cessation alone, but others have progressed despite cessation of smoking. Glucocorticoids have been reported to be beneficial in a number of cases, although relief may be temporary. The overall survival rate is approaching 90%. Mortality rate is between 6% and 28% with a rare progression to severe fibrosis[15].

In a systematic review of reported cases of PID, about 50% improved with smoking cessation and systemic glucocorticoid therapy. Overall survival was 70 to 88% after



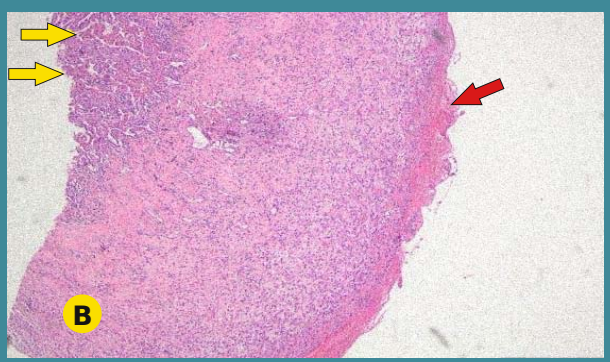


Figure 9. *Credits: Diagnostics – Interesting images "Sequence of rare diagnoses in a young patient: altitude barotrauma hemopneumothorax and desquamative interstitial pneumonia" - Dr. Beatrice Mahler*
A: *Desquamative pneumonia (DIP-like) reaction – endoalveolar collections of macrophages with intracyto- 89 plasmic brown pigment are present (yellow arrows); HE, 100x; HE = standard stain (hematoxylin-eosin)*

B: *Fibrinous pleurisy in the process of organization – the visceral pleura is thickened and on its surface there are eosinophilic deposits offibrin (red arrow). The underlying lung parenchyma presents numerous macrophages with intracytoplasmic brown pigment (yellow arrows) inside the alveolar spaces-desquamative pneumonia – DIP-like reaction; HE, 40x.*





Figure 10.
HRCT at the time of the diagnosis
12 months apart

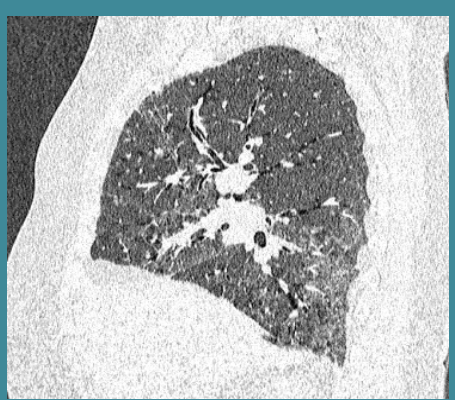




Figure 10.
18 months after the diagnosis
24 months after the diagnosis



10 years. Several studies have demonstrated 100% survival rates for DIP, but to some extent this reflects a trend to exclude patients with associated fibrosis[16-17].

RB/RB-ILD and DIP are the abnormal accumulation of macrophages in the air spaces, and the key features that differentiate between the two are the distribution and extent of macrophages accumulation (Table 1). The histological feature of DIP is extensive, diffuse and uniform airspace fillingby smoker's macrophages[16-17].

RB/RB-ILD and DIP remain separately classified because of their differences in clinical entities, radiological manifestations and response to treatment. The progression to respiratory failure is more likely to appear for patients with DIP than with RB-ILD. Transbronchial lung cryobiopsy (TBLC) is a new technique to obtain specimens and has been used for ILD diagnosis in recent years, but thoracoscopy biopsy is required mostly when other investigations are non-specific[18].

The therapeutic approach is mainly smoking cessation which can lead to remission in some cases. Long-term corticosteroid therapy has been reported to be most effective in the treatment of DIP[21]. Combining the treatment with corticosteroids can decrease bronchial wall thickening extend, centrilobular nodules, ground glasses opacities with 43%. The living rate goes up to 75% after 7 years, making it a benign entity. The progression to sever fibrosis is rare if given corticosteroid treatment 40-60mg/day for 6 weeks. The second clinical case we bring to your attention is the case of a 52 year old woman, heavy smoker, 30 packs-years, with professional exposure in a steel processing factory for 23 years and with no relevant drug history. She was brought to the hospital for progressive effort dyspnea, cough and minimal hemoptysis for 2 months prior. Her comorbidities are hypertension and dyslipidemia.

The PFT show moderated mixed ventilatory dysfunctions with FVC 71,2% and FEV1 63,2% of the predicted value, with a cardiac evaluation with EF 55% and PAPs 45mmHg. She has been evaluated by the thoracic surgeon with indication for surgical lung biopsy. Thus, the biopsy has shown fragments of lung parenchyma with modified architecture by thinning of the interalveolar septs, resulting in enlarged air spaces. The alveoli contain numerous macrophages with golden brown pigment and relatively common erythrocytes. The conclusion was unclear, DIP/RB-ILD, whereas the findings in DIP overlap with those in RB-ILD.

The physical exam describes an overweight middle age female with suffering facies, tachycardia, without pulmonary rales and oxygen saturation of 94%aa. A further step was the treatment with oral corticosteriods 32mg/day, with progressive decrease of the dose. During the 2 years follow-up, the patient was evaluated at 2, 6, 18 and 24

months, including HRCT exam, every time. Despite the firm recommendation to stop smoking, the patient is still a heavy smoker she has persistent dyspnea, and PFT show a decrease of the DLCO percentage from 41,6% to 32,6% within 24 months. She is currently undergoing inhalation treatment with tiotropium and olodaterol (Figure 10,11).

It is visible that prevention strategies in ILD remain at an early stage of development, but with clear opportunities for a rapid expansion.

Short-term (next 5 years) and long-term opportunities (next 10 years) are available to develop appropriate primary prevention strategies. A number of research topics need to be addressed before conducting primary prevention trials, and these priority research areas include: improve strategies for early detection of disease (phenotype and endotype), define proxy measures and risk-stratification biomarkers (genomics and imaging), determine risk factors for the development of subclinical ILD, determine the natural history of different forms of ILD (longitudinal outcomes), so as to enable interpretation of potential outcome and design safe interventions that can be tested in individuals affected with subclinical ILD[20].

An alternative approach is to target high-risk populations, such as older adults with a history of smoking. Patients who are current or former smokers have an increased risk of developing lung cancer or parenchymal lung diseases (e.g. ILD and chronic obstructive pulmonary disease). Annual screening for lung cancer using low-dose CT is recommended for people considered at high risk based on age and smoking history.

References:

1. Carlyne D Cool, MD, Idiopathic interstitial pneumonias: Classification and pathology, 2023

2. Int J. Environ Res Public Health. Tobacco Smoke Induces and Alters Immune Responses in the Lung Triggering Inflammation, Allergy, Asthma and Other Lung Diseases: A Mechanistic Review, 2018

3. Am J Pathol, Essential Role of Osteoponin in Smoking-Related Interstitial Lung Diseases, 2009

4. Ann Glob Health, Interstitial Lung Diseases in Developing Countries, 2019

5. The World Health Organization. Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease, 2016

6. Jeffrey R. Galvin, MD,Teri J. Franks, MD, Smoking Related Lung Disease, 2009

7. Alicja Sieminska, Krzysztof Kuziemski, Respiratory Bronchiolitis-interstitial lung disease, 2014

8. Park JS, Brown KK, Tuder RM, et al. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr. 2002

9. Remy-Jardin M, Remy J, Gosselin B, et al. Lung parenchymal changes secondary to cigarette smoking: pathologic-CT correlations, 1993

10. Joshua Portnoy, MD, Kevin K, Brown MD, Respiratory Bronchiolitis-Interstitial Lung Disease, CHEST Journal, 2007

11. Craig PJ, Wells AU, Doffman S, Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking, 2004

12. Athol Wells, Andrew G Nicholson, Challenges in Pulmonary Fibrosis, 2007

13. Rebanta K Chakraborty, Hajira Basit, Sandeep Sharma, Desquamative Interstitial Pneumonia, 2023

14. Hartman TE, Primack SL, Swensen SJ, Desquamative interstitial pneumonia: thin-section CT findings in 22 patients, 1993

15. Ryu JH, Myers JL, Capizzi SA, Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease, 2005

16. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia, 1989

17. Vassallo R, Jensen EA, Colby TV, The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis, 2003

18. BMC Pulm Med, Implementation of transbronchial lung cryobiopsy in tertiary referral center for interstitial lung diseases: a cohort study on diagnostic yield, complications and learning curves, 2021

19. So Hyeon Bak,Ho Yun Lee, Overlaps and uncertainties of smoking-related idiopathic interstitial pneumonias

20. Ivan O. Rosas, Fernando J. Martinez, Interstitial Lung Disease: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases, 2014

21. Beatrice Mahler, Sequence of rare diagnoses in a young patient: altitude barotrauma hemopneumothorax and desquamative interstitial pneumonia, Diagnostics, 2022.