

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Desquamative interstitial pneumonia with clinical, radiological and histologic correlation

Miras Medenica, BSc, MBChB^{a,*}, Milic Medenica, PhD^b

^a Stepping Hill Hospital, Stockport NHS Foundation Trust, Poplar Grove, Hazel Grove, Stockport SK2 7JE

^b Hospital for Lung Diseases, Brezovik, Njegoseva bb, Niksic 81400, Montenegro

ARTICLE INFO

Article history:

Received 9 December 2018

Revised 25 January 2019

Accepted 27 January 2019

Available online 13 February 2019

Keywords:

Respiratory bronchiolitis-associated interstitial lung disease

Desquamative interstitial pneumonia

Idiopathic interstitial pneumonia

Smoking

ABSTRACT

Respiratory bronchiolitis-associated interstitial lung disease (ILD), desquamative interstitial pneumonia (DIP), and pulmonary Langerhans cell histiocytosis are entities of smoking-related ILD. While clinically regarded as 2 separate forms of idiopathic interstitial pneumonia, DIP, and respiratory bronchiolitis-associated ILD are thought to be representing ends of a continuous spectrum of disease that primarily affects tobacco smokers. This case report presents a 53-year-old female patient who has 58 pack-year smoking history who has been experiencing a dry cough and epigastric pains for 2 years. Open-lung biopsy is performed and histopathology indicated smoking-related interstitial fibrosis. The patient did not stop smoking, which after a year leads to significant clinical deterioration with a notable decrease in diffusion for carbon monoxide capacity. Upon smoking cessation and treatment with corticosteroids, a significant clinical improvement is achieved. In smokers complaining of cough and reduced exercise tolerance and in whom evidence of interstitial fibrosis is demonstrated radiologically, DIP should be considered as a differential diagnosis. Smoking is the exclusive etiologic factor of pathogenesis of DIP.

© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license.

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

The spectrum of smoking-related interstitial lung disease (ILD) encompasses respiratory bronchiolitis-associated ILD (RB-ILD) and desquamative interstitial pneumonia (DIP) [1]. While clinically regarded as 2 separate forms of idiopathic interstitial pneumonia, DIP and RB-ILD are thought to be

representing ends of a continuous spectrum of disease that primarily affects tobacco smokers. The diagnostic distinction persists owing to evidence demonstrating that DIP and RB-ILD have natural histories and prognoses that differ. The pathologic feature of both diseases is accumulation of golden-brown pigment in macrophages in the cytoplasm. RB-ILD reflects inhalational exposure as findings are centered around the bronchioles with peribronchiolar fibrosis and inflammation. On the other hand, DIP affects the airways and extends into the alveolar space and can include mild-to-moderate interstitial fibrosis. As DIP and RB-ILD reactions are often

* Corresponding author.

E-mail address: miras.medenica@doctors.org.uk (M. Medenica).

<https://doi.org/10.1016/j.radcr.2019.01.016>

1930-0433/© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

frequent and incidental findings in the lung tissue of smokers, formal clinical diagnosis of these conditions is dependent upon the presence of significant symptoms, radiographic changes, and functional impairment. When taken into account together, DIP and RB-ILD account for up to 15%-20% of patients with idiopathic interstitial pneumonias biopsies [2–5]. Patients diagnosed with RB-ILD and DIP are typically male, in their 40s or 50s, with an average of a 30 pack-year smoking history.

Case report

This case report presents a 53-year-old female patient who has 58 pack-year smoking history. She has been experiencing a dry cough and epigastric pains for 2 years. There was no history of hemoptysis, weight loss, fevers, or night sweats.

Past medical history consists of type 1 diabetes mellitus, cervical cancer excision in 2005, and a uterine fibroid excision in 2009.

Clinical examination revealed reduced air entry throughout both lungs and no signs of peripheral edema, hemorrhage or bruises, no palpable lymphadenopathy. Chest X-ray on admission has shown enhanced reticularity on the whole, while high resolution CT of the chest demonstrated diffuse and bilateral polymorphic lesions, pulmonary and centrilobular nodules, cystic changes, and distorted pulmonary parenchyma—suggestive of interstitial fibrosis.

Pulmonary function tests demonstrated mild obstructive pattern and moderate decrease in diffusion capacity for carbon monoxide. Transbronchial lung cryobiopsy was not possible due to technical limitations, thus open-lung biopsy was decided to be the best diagnostic modality. Open-lung biopsy was subsequently performed and histopathology indicated smoking-related interstitial fibrosis (DIP). Patient was treated with prednisolone 20 mg 3 times a day and smoking cessation was advised. Despite the advice, patient has continued to smoke, which after a year leads to significant clinical deterioration with coughing bouts, dyspnoea, reduced exercise tolerance associated with a notable decrease in diffusion capacity for carbon monoxide. Auscultation of the chest reveals reduced air entry throughout. Pulmonary function tests demonstrate a restrictive pattern of pulmonary ventilation of moderate degree. Continuous oxygen therapy was prescribed along with corticosteroids. Seven to eight months upon stopping smoking values of arterial blood gases have normalized and continuous oxygen therapy was stopped.

Hematology, biochemistry, and immunology: white cell count—5.7; ery—4.93; Hb—146; PLT—188; ESR—28; glycemia—17.6 mmol/l; acidum uricum—402; AST—82; ALT—151; gamma GT—122; hemoglobin A1c—9.8. Thyroid function tests all within normal limits; antithyroid peroxidase antibody—13.1. Antinuclear antibody—negative; antineutrophil cytoplasmic antibody—negative.

Pulmonary function tests on first admission: spirometry: forced vital capacity—3.13 L (103%); forced expiratory volume 1—2.16 L (83%); FEV1/FVC—69.03%.

Diffusion capacity for carbon monoxide (DLCO): 58%; carbon monoxide transfer coefficient (KCO): 61%.

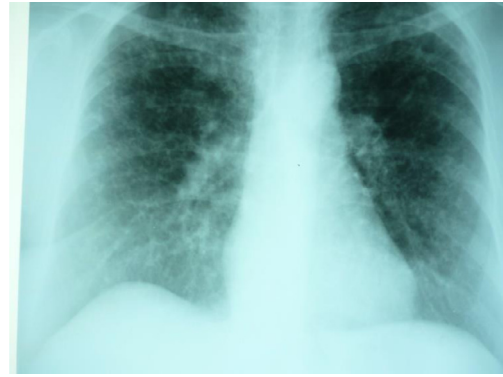


Fig. 1 – Chest X-ray on admission demonstrates enhanced reticularity on the whole.

Pulmonary function tests on second admission: forced vital capacity—1.62 L (58%); forced expiratory volume 1—1.17 L (50%); FEV1/FVC—72.2%. Diffusion capacity for carbon monoxide (DLCO)—33.4% (3.86 L); carbon monoxide transfer coefficient (KCO)—58%. Arterial blood gas: pO₂—48.3 mmHg; pCO₂—35.1 mmHg; oxygen saturation—83.9%.

Echocardiogram: Normal aorta and mitral valve and right ventricle, with a left ventricle of normal dimensions, good contractility, and normal wall thickness. Ejection fraction was found to be 63%.

Radiology: Figures 1 and 2.

Histopathology: Figure 3.

Discussion

DIP and RB-ILD are parts of a spectrum of disorders that affects smokers. Patients often report nonspecific symptoms of nonproductive cough and progressive dyspnoea. Physical examination may be unremarkable but also can reveal dry inspiratory crackles and finger clubbing as seen in other forms of ILD. Extrapulmonary features are usually absent.

Tobacco smoke exposure accounts for most of the cases of DIP and RB-ILD, despite them being categorized as idiopathic interstitial pneumonia. Furthermore, it has been reported that in up to 90% of RB-ILD and DIP cases, tobacco smoke is a causative agent [2,6]. Thus, it is of significance that a number of exposures are reported to have an association with DIP include marijuana smoking, beryllium, diesel fume, fire extinguisher powder, copper, asbestos, and certain chemicals used in textile processing [7–9]. In addition, DIP has been reported as a complication of autoimmune diseases such as rheumatoid arthritis and scleroderma [8,10] and has also occurred in association with infections including cytomegalovirus, hepatitis C, and aspergillus [11,12]. Genetic factors do not seem to have a dominant role.

Patients with RB-ILD often exhibit a restrictive physiological pattern with accompanying reduction in DLCO. However, given that the pathology is bronchiolocentric in nature, a mixed pattern with some elements of obstructive pattern can also be observed. Patients diagnosed with DIP

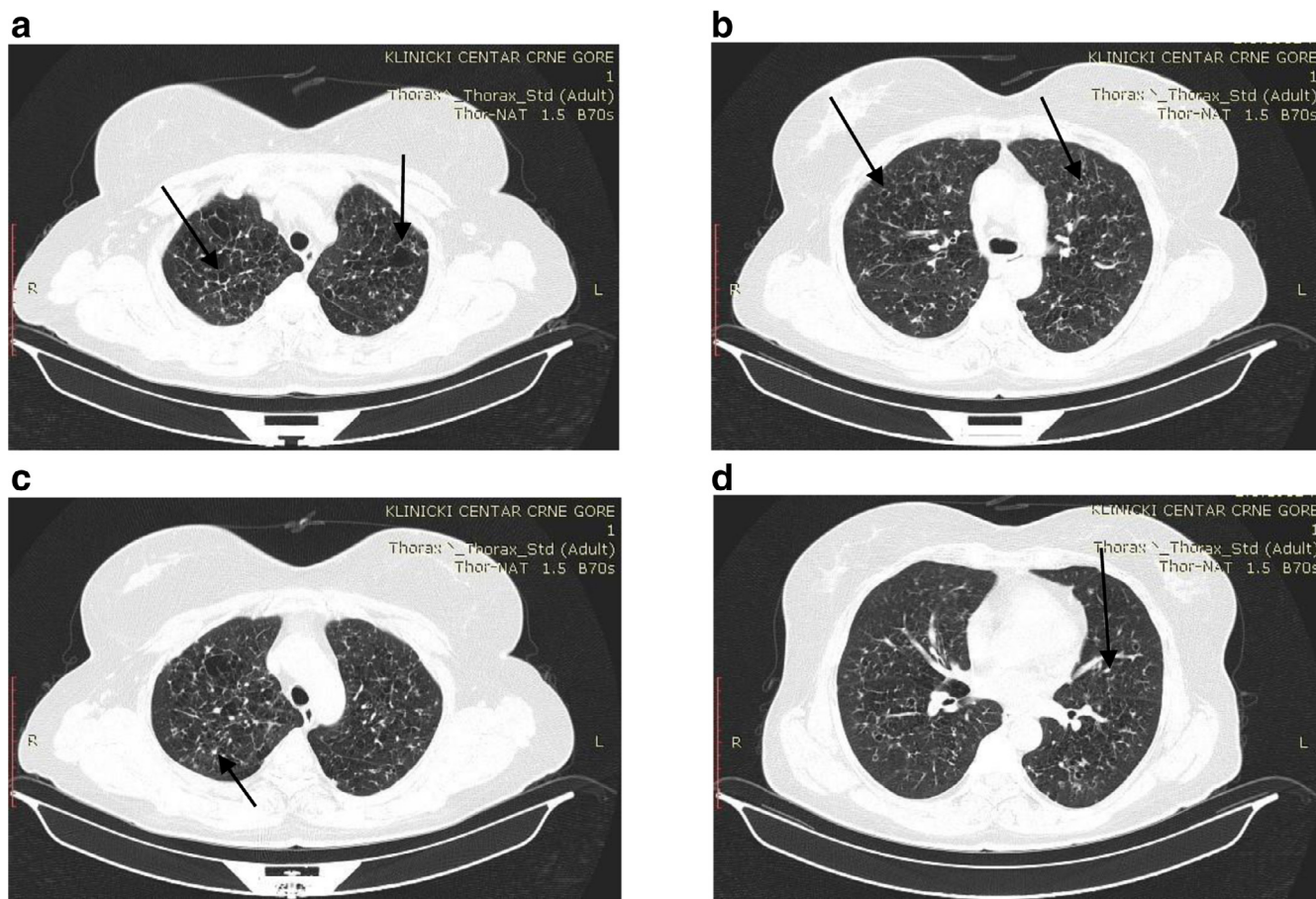


Fig. 2 – High-resolution CT of the chest: (a) a few thin-walled lesions and a majority of thick-walled lesions; (b) cystic changes that range from a couple of millimeters to 2 cm in diameter. Furthermore, (c) pulmonary nodules and (d) bleak centrilobular nodules measuring up to 5 mm in diameter are demonstrated. In addition, polymorphic lesions are present diffusely and bilaterally, with the exception of outermost dorso-basal aspects of both lungs.

generally demonstrate a restrictive ventilatory defect accompanied with reduction in diffusion capacity. Hypoxemia may be a marker of more severely affected patients, which was one of the manifestations of the disease in our patient 1 year after the diagnosis of DIP has been made. Occasionally lung volume impairments and spirometry seem less severe compared to the patient's clinical state.

Chest X-ray changes in DIP are usually quite faint; however, nonspecific, hazy, ground-glass opacities may be present. The most common CT finding are ground-glass opacities that are usually peripheral (Fig. 2), but can also be diffuse [13]. Other findings on CT include small cysts and reticular markings, which may be indicative of a component of fibrosis [13,14]. Furthermore, more extensive fibrotic changes such as traction bronchiectasis can be observed, which was one of the findings demonstrated in this case report. Honeycombing changes are rare. Moreover, emphysema and bronchial wall thickening can also be a feature of the radiological findings in DIP [13].

RB-ILD imaging findings are usually subtle and are not visualized on chest X-ray. CT findings include subtle, upper lobe predominant or diffuse patchy ground-glass densities, and centrilobular ground-glass nodules [15–17]. Concomitant find-

ings that are associated with cigarette smoking can also be present such as tissue rarefaction, bronchial wall thickening from chronic bronchitis, and bullae reflecting emphysema. The main alternative diagnosis that is to be considered in a patient who has centrilobular ground-glass nodules on CT of the chest is subacute hypersensitivity pneumonitis.

Diagnosing DIP and RB-ILD requires a comprehensive clinical assessment that integrates history, examination, PFTs, and HRCT. Due to the fact that the histopathology of DIP and RB-ILD may be present in the lung tissue of asymptomatic smokers, pathological findings alone are not diagnostic. Bronchoscopy can be helpful by ruling out other processes resembling DIP or RB-ILD. Broncho-alveolar lavage demonstrates characteristic pigmented macrophages, while a pronounced eosinophilia has been reported to feature in the broncho-alveolar lavage specimens of some DIP patients. However, for both DIP and RB-ILD surgical lung biopsy might be necessary in order to formally establish the underlying diagnosis as well as to exclude alternative causes of the symptomatology.

Hallmark of the pathological findings in RB-ILD and DIP is the accumulation of pigmented macrophages, also referred to as smoker's macrophages. These macrophages contain iron

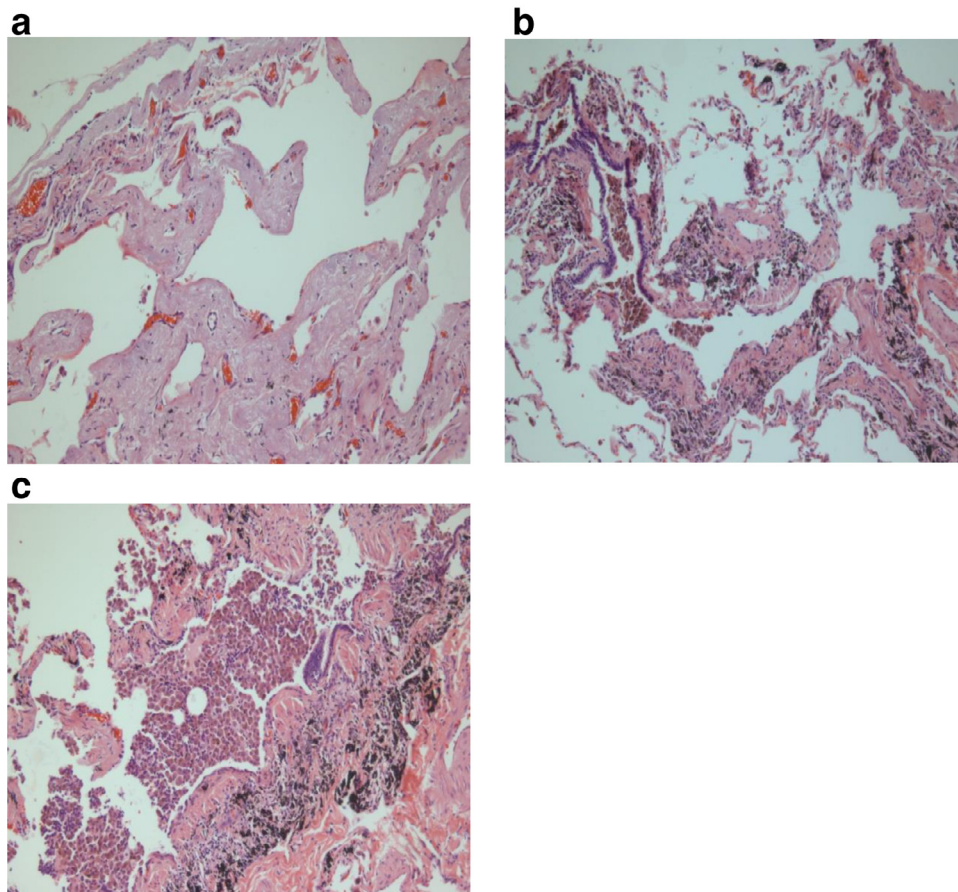


Fig. 3 – Open-lung biopsy. Hematoxylin-eosin stain; 200x findings of fibrosis of emphysematous cavities (a), respiratory bronchiolitis and deep parenchymal fibrosis (b), accumulation of brown alveolar macrophages—DIP-like appearance (c) correspond to lung changes associated with smoking, namely smoking-related interstitial fibrosis.

and display a glassy cytoplasm that is eosinophilic and has a fine granular, yellowish-brown pigment that most likely contains components of tobacco smoke. In our patient's case, lung biopsy revealed interstitial inflammation, fibrosis, respiratory bronchiolitis, bullous emphysema, and areas of focal atelectasis. Alveolar spaces were filled with a mass of brown alveolar macrophages.

Patients with RB-ILD or DIP characteristically have less fibrosis and have a more favorable prognosis compared to idiopathic pulmonary fibrosis, possibly partly owing to smoking cessation and corticosteroids that have often proven to be effective therapies in RB-ILD and DIP patients [4,5,18]. Progressive disease is uncommon in RB-ILD and is a more often occurrence in patients with DIP. A study found that 33% of DIP patients experienced objective radiographic or physiological improvement, while 64% of RB-ILD patients have been found to achieve an objective improvement radiologically and physiologically [2]. One year after diagnosing DIP in our patient, she has experienced a significant deterioration of lung function due to continued smoking. Furthermore, another study established that 26% of patients with DIP passed away, compared to no patients having a fatal outcome in RB-ILD, which confirms the findings of prior work by Carrington and Yousem [19–21].

The mainstay of treatment for these diseases is smoking cessation. For patients with mild-to-moderate symptoms and functional impairment, a period of observation after cessation of tobacco smoking is reasonable. Many patients stabilize and clinically improve; however, adjuvant corticosteroid treatment often limits the interpretation of the degree of efficacy of smoking cessation alone as a treatment [4] and earlier studies by Carrington and Yousem have not managed to characterize comprehensively the effect of smoking cessation. Additional limitations that complicate assessment of improvement are the presence of other lung pathologies that are related to smoking such as emphysema, a condition of which contribution to impairment will generally not respond to any intervention.

Patients who suffer from severe impairment and symptoms may benefit from therapy with systemic corticosteroids. A 6- to 9-month course of treatment starting at 40-60 mg/daily for 6 weeks is a reasonable option. The role of alternative immunosuppressant medications in RB-ILD and DIP that are utilized in other ILDs has been less well defined. However, macrolide antibiotics have been reported to be an alternative effective steroid-sparing treatment in DIP [22]. Lung transplantation may be a necessity for patients with severe and

progressive disease. Post-transplant recurrence of disease has been reported [21].

REFERENCES

- [1] Hartman TE, Tazelaar HD, Swensen SJ, Müller NL. Cigarette smoking: CT and pathologic findings of associated pulmonary diseases. *Radiographics* 1997;17:377–90.
- [2] Ryu JH, Myers JL, Capizzi SA, Douglas WW, Vassallo R, Decker PA. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease. *Chest* 2005;127(1):178–84.
- [3] Davies G, Wells AU, du Bois RM. Respiratory bronchiolitis associated with interstitial lung disease and desquamative interstitial pneumonia. *Clin Chest Med* 2004;25(4):717–26 vi.
- [4] Caminati A, Cavazza A, Sverzellati N, Harari S. An integrated approach in the diagnosis of smoking-related interstitial lung diseases. *Eur Respir Rev* 2012;21(125):207–17.
- [5] Caminati A, Harari S. Smoking-related interstitial pneumonias and pulmonary Langerhans cell histiocytosis. *Proc Am Thorac Soc* 2006;3(4):299–306.
- [6] Craig PJ, Wells AU, Doffman S, Rassl D, Colby TV, Hansell DM, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. *Histopathology* 2004;45(3):275–82.
- [7] Abraham JL, Hertzberg MA. Inorganic particulates associated with desquamative interstitial pneumonia. *Chest* 1981;80(1 suppl):67–70.
- [8] Aoki Y, Fukuoka M, Naitoh K, Kohsa K, Kawashima M, Hayashi S. Desquamative interstitial pneumonitis accompanied by a variety of autoimmune abnormalities in an individual with a history of asbestos exposure. *Nihon Kokyuki Gakkai Zasshi* 1998;36(8):717–21.
- [9] Freed JA, Miller A, Gordon RE, Fischbein A, Kleinerman J, Langer AM. Desquamative interstitial pneumonia associated with chrysotile asbestos fibres. *Br J Ind Med* 1991;48(5):332–7.
- [10] Ishii H, Iwata A, Sakamoto N, Mizunoe S, Mukae H, Kadota J. Desquamative interstitial pneumonia (DIP) in a patient with rheumatoid arthritis: is DIP associated with autoimmune disorders? *Intern Med* 2009;48(10):827–30.
- [11] Schroten H, Manz S, Kohler H, Wolf U, Brockmann M, Riedel F. Fatal desquamative interstitial pneumonia associated with proven CMV infection in an 8-month-old boy. *Pediatr Pulmonol* 1998;25(5):345–7.
- [12] Hasegawa H, Nakamura Y, Kaida Y, Enomoto N, Hashimoto D, Inui N, et al. A case of desquamative interstitial pneumonia associated with hepatitis C virus infection. *Nihon Kokyuki Gakkai Zasshi* 2009;47(8):698–703.
- [13] Doan ML, Guillerman RP, Dishop MK, Nogee LM, Langston C, Mallory GB, et al. Clinical, radiological and pathological features of ABCA3 mutations in children. *Thorax* 2008;63(4):366–73.
- [14] Iskandar SB, McKinney LA, Shah L, Roy TM, Byrd RP Jr. Desquamative interstitial pneumonia and hepatitis C virus infection: a rare association. *South Med J* 2004;97(9):890–3.
- [15] Lynch DA. High-resolution CT of idiopathic interstitial pneumonias. *Radiol Clin North Am* 2001;39(6):1153–70.
- [16] Heyneman LE, Ward S, Lynch DA, Remy-Jardin M, Johkoh T, Muller NL. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? *AJR Am J Roentgenol* 1999;173(6):1617–22.
- [17] Attili AK, Kazerooni EA, Gross BH, Flaherty KR, Myers JL, Martinez FJ. Smoking-related interstitial lung disease: radiologic-clinical-pathologic correlation. *Radiographics* 2008;28(5):1383–96 discussion 1396–98.
- [18] Vassallo R, Ryu JH. Tobacco smoke-related diffuse lung diseases. *Semin Respir Crit Care Med* 2008;29(6):643–50.
- [19] Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. *Mayo Clin Proc* 1989;64(11):1373–80.
- [20] Carrington CB, Gaensler EA, Coutu RE, FitzGerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978;298(15):801–9.
- [21] Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. Usual and desquamative interstitial pneumonia. *Chest* 1976;69(2 Suppl):261–3.
- [22] Faverio P, Bini F, Vaghi A, Pesci A. Long-term macrolides in diffuse interstitial lung diseases. *Eur Respir Rev* 2017;26 170082 [<https://doi.org/10.1183/16000617.0082-2017>].