CASE REPORT

Respiratory bronchiolitis-associated interstitial lung disease – an unexpected form of idiopathic interstitial pneumonia in a young male

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Abstract

Cigarette smoking is the most frequently encountered risk factor for chronic obstructive pulmonary disease and lung cancer. The latest *American Thoracic Society/European Respiratory Society* classification of idiopathic interstitial pneumonia includes two entities related to smoking habits: respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia. The new approach to diagnosis is to combine pathological pattern with clinical and radiological data. Lung biopsy is no longer considered the "gold standard" for diagnosis, but as a part of the diagnosis, which shall be set only after the pulmonologist, radiologist and pathologist reviewed all clinical, imaging and pathological aspects. We report a case of a young male, who complained of respiratory symptoms, had normal volumes and flows on lung function tests, moderately reduced transfer factor for carbon monoxide and "ground glass" attenuation on high-resolution computed tomography. Because the patient had exposure to contact with parrots, hypersensitivity pneumonitis was considered, but the broncho-alveolar lavage was without lymphocytosis. Open lung biopsy confirmed the diagnosis of respiratory bronchiolitis-associated interstitial lung disease, a rarely described entity in the medical literature. The patient had a good clinical outcome after smoking cessation.

Keywords: respiratory bronchiolitis-associated interstitial lung disease, lung biopsy, cigarette smoking.

Introduction

Cigarette smoking is the most frequently encountered risk factor for chronic obstructive pulmonary disease (COPD) and lung cancer [1]. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is also a smoking-related disease, much less known and likely underdiagnosed. RB-ILD is part of major idiopathic interstitial pneumonias (IIPs) along with idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP) [2]. The positive diagnosis of a particular form of IIP needs a multidisciplinary approach and lung biopsy remains the gold standard in cases where not all criteria are met. It is a rare mild inflammatory disease that combines pathological changes of respiratory bronchiolitis (RB) with clinical evidence of interstitial lung disease [3]. RB-ILD has a variable prognosis, some cases being self-limited after smoking cessation [4].

We report this case because of the high difficulty sustaining positive diagnosis, requiring open lung biopsy in a young man.

Case presentation

We present the case of a 39-year-old man, with a history of 25 pack-years of smoking, with no occupational exposure but with home exposure to pets (two Siamese cats and two parrots), who was admitted to hospital in August 2014 for progressive dyspnea since November 2013, thoracic pain on the left, posterior part, and dry cough. In the last months, he associated heavy nocturnal sweating. The physical examination upon hospital admission did not show any significant changes: non-febrile, good overall condition, normal weight [body mass index (BMI) 24.4 kg/m^2], normal thoracic examination, and no added crackles on auscultation. Oxygen saturation was 97% while breathing room air, blood pressure was 120/80 mmHg, and heart rate 70 beats/min. Biological tests were normal, and human immunodeficiency virus (HIV) test was negative. The chest X-ray did not reveal any particular findings that could explain dyspnea. Lung function tests showed normal volumes and flows, and a moderate reduction of diffusing capacity or transfer factor for carbon monoxide (DL$_{CO}$ or TL$_{CO}$) at 56% predicted.

Thoracic high-resolution computed tomography (HRCT) showed numerous patchy areas of ground-glass attenuation (Figure 1). Because the patient had exposure to parrots, hypersensitivity pneumonitis was suspicioned. Broncho-scopy showed no lesions of the mucosa. Broncho-alveolar lavage (BAL) has been performed in the area of the middle lobe and showed an increased total number of cells (20.8 million), with normal cellularity: 82.8% macrophages, 8.8% lymphocytes, 7.8% neutrophils, and 0.6% eosinophils. BAL was negative for bacteria (including *Mycobacterium tuberculosis*), fungi or tumor cells. The macrophages were tan brown (smokers' macrophages). Since BAL sustained

no diagnosis, open multi-centric lung biopsy was performed from the upper and lower left lobes (the patient consented to the intervention).


Figure 1 – *CT image showing bilateral patchy areas of ground-glass attenuation in the upper lung lobes (the most common finding).*

Pathology report of the two fragments of biopsy from the left lower lobe (40/20/0.5 mm) with patchy areas of discrete consolidation and left upper lobe (40/30/10 mm), with reduced crackles and elasticity were found on gross examination. The microscopic examination was performed on pieces of lung biopsy included in paraffin and stained with Hematoxylin–Eosin (HE) and green light trichrome, the Goldner–Szekely (GS) technique. For the specific highlighting of macrophages, there was used the immuno-histochemical immunomarking with anti-CD68 antibody (monoclonal mouse anti-human CD68, clone KP1, 1/100 dilution, Dako).

The microscopic examination revealed lung parenchyma characterized by an important accumulation of intra-alveolar and intra-bronchiolar macrophages, associated with cellular bronchiolitis lesions (Figure 2, a and b). The macrophages had abundant cytoplasm and were loaded with golden-brown pigment (Figure 3). In some peri-bronchiolar areas, alveolar septa were mildly thickened and contained mononuclear inflammatory infiltrates and minimal fibrosis (Figures 4 and 5). Under the pleura, lung parenchyma had thinned and broken alveolar septa, resulting in dilated air spaces (areas of subpleural emphy-sema). Pleura was discreetly collagenised and contained a small amount of lymphocyte inflammatory infiltrate. Lymph node from the inferior vein (0.6 cm, whitish) had anthracosis and discreet follicular hyperplasia. The final diagnosis was of RB-ILD, confirming the clinical hypothesis of a major form of IIP in a smoker.
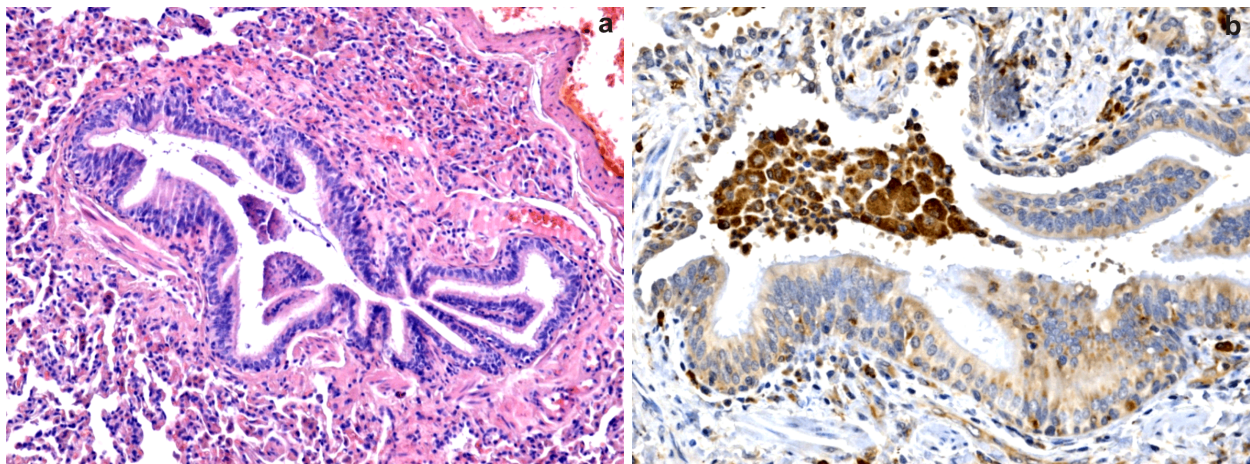
Figure 2 – *(a) Respiratory bronchiole with intraluminal tan brown macrophages (smokers' macrophages) and parietal fibrosis (HE staining, ×100); (b) Respiratory bronchiole with intraluminal macrophages (Anti-CD68 antibody immuno-marking, ×200).*
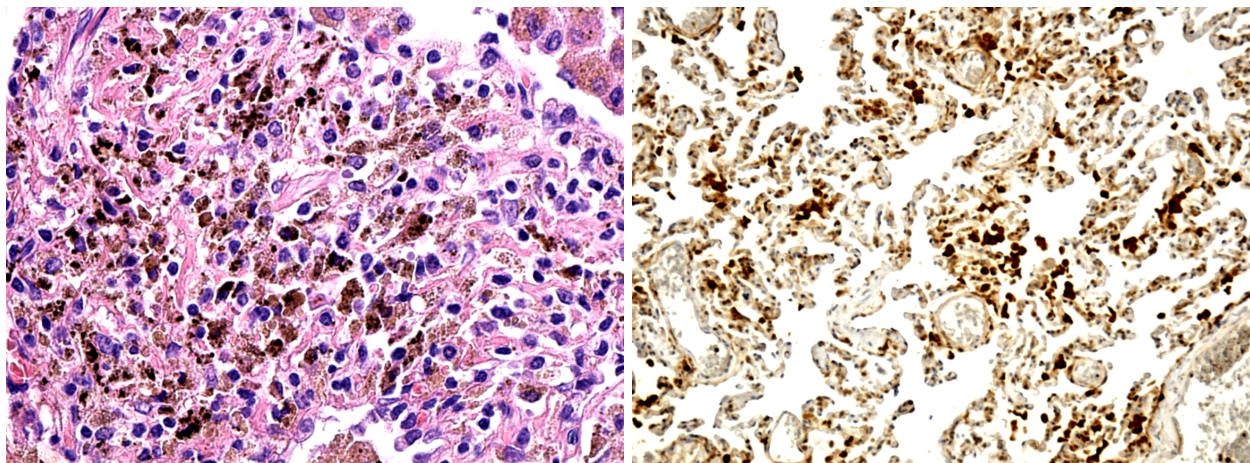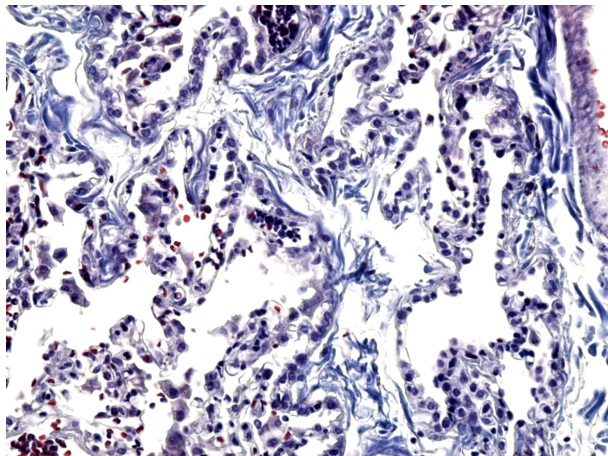

Figure 3 – *Tan brown macrophages (smokers' macro-phages) inside alveolar spaces (HE staining, ×400).*
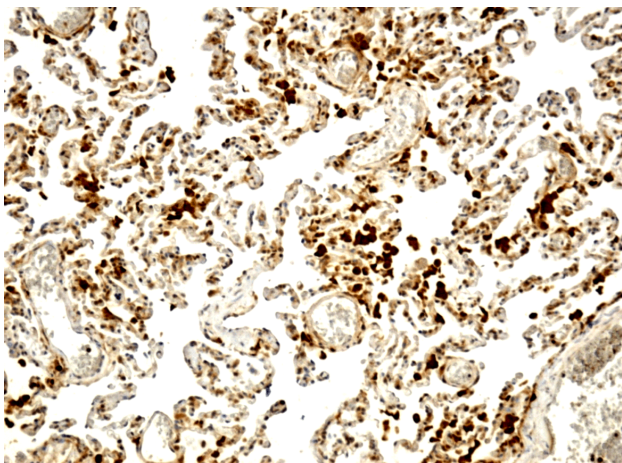
Figure 4 – *Parenchymal lung with thickened alveolar septa by the presence of numerous macrophages (Anti-CD68 antibody immunomarking, ×200).*

Figure 5 – *Interstitial peribronchiolar fibrosis (GS trichrome staining, ×200).*

The patient was advised to quit smoking. He did not receive corticosteroid treatment considering the fact that we had to monitor the clinical evolution of the lung function after withdrawal of the risk factor. Six months later the patient showed a clinical and radiological improvement with an increase in exercise tolerance and normalized DL_{CO}. No relapses occurred in the 18 months of the survey.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

⊟ Discussion

The association between RB on lung biopsy and ILD was described by Myers, in 1987 [5]. The patients with RB-ILD, smokers or former smokers, are 30–40 years old and complain especially of dyspnea on exertion and cough. The clinical or serological evidence of underlying connective tissue disease or significant family history are absent. Pulmonary function test frequently reveals mixed obstructive and restrictive dysfunction with moderately reduced diffusing capacity (DL_{CO}) [4]. We present the case of a young man with progressive dyspnea, normal lung volumes and flows on lung function tests and a moderate decrease of DL_{CO}, with the suspicion of interstitial lung disease on HRCT due to the presence of patchy areas of ground glass attenuation. The main findings of RB-ILD on HRCT are: centrilobular nodules, ground-glass attenuation, central and peripheral bronchial wall thickening, but rarely, intra-lobular fine linear-reticular opacity, emphysema, traction bronchiolectasis may appear [6, 7]. Because the patient had home exposure to parrots, hypersensitivity pneumonitis (HP) was suspicioned, but BAL without lymphocytosis ruled out this hypothesis (in HP lymphocytes are often higher than 50% of the total cell number, with less than 1 CD4/CD8 ratio) [8, 9]. BAL is non-specific in RB-ILD, but it is performed to exclude other diseases [*e.g.*, HP, Langerhans cell histiocytosis (LCH), and sarcoidosis].

Lung biopsy, which can differentiate between interstitial lung diseases, share the same clinical and radiological findings, is rarely indicated. In the same time, for a patient less than 50 years old, lung biopsy is useful to exclude neoplastic (carcinomatosis) and infectious (miliary tuber-culosis) diseases, to identify the pattern of ILD, and to predict the response to therapy [10]. The chronic form of HP, DIP, IPF, NSIP, AIP, lymphoid interstitial pneumonia (LIP), COP, combined pulmonary fibrosis and emphysema (CPFE), and sarcoidosis were taken into consideration. Due to the large number of diagnostic possibilities, open lung biopsy was considered as the next step in diagnosis. The pathology report confirmed the diagnosis of RB-ILD.

The presence of tan-brown macrophages (or smokers' macrophages) in the lumen of the respiratory bronchioles and alveoli, a submucosal and peribronchiolar infiltrate of lymphocytes and histiocytes, and peribronchiolar slight fibrosis with thickening of the adjacent alveolar walls are the characteristic pathological findings in lung biopsy [11]. Other interstitial lung diseases like DIP, HP, LCH need to be excluded (Table 1). DIP shares the similar pathogenesis and pathological changes but affects the lung in a more uniform and diffuse manner than RB-ILD [4].

Table 1 – *Differential diagnosis of respiratory bronchiolitis–interstitial lung disease*

Disease	Histological findings	Distribution	Comments
RB/ RB-ILD	▪ Macrophages containing fine, granular yellow-brown cytoplasmic pigments ("smoker's macrophages/tan brown macrophages") [12]; ▪ Mild lymphocytic inflammation and mild fibrosis; ▪ Architectural distortion; ▪ Centrilobular emphysema.	▪ Lumens of respiratory bronchioles and peribronchial air spaces, perialveolar ducts; ▪ Submucosal and peribronchioar; ▪ Bronchiolar and peribronchiolar fibrosis that expands contiguous alveolar septa.	▪ In heavy smokers, the pigment becomes coarser resembling hemosiderin; ▪ Distinction between RB and RB-ILD on clinical evidence of ILD.
DIP	▪ Abundant accumulation of "smoker's macrophages"; ▪ Interstitial inflammation and/or fibrosis [13].	▪ Alveolar spaces associated with interstitial inflammation and/or fibrosis; ▪ More diffuse lesions within pulmonary acini.	▪ Greater extent of interstitial fibrosis, lymphoid follicles and eosinophilic infiltration in patients with DIP compared with RB [14].
COP	▪ Inflammatory and fibrotic process, 20% foamy alveolar MFs (may simulate DIP); ▪ Fibrosis is absent; ▪ Preserved architecture.	▪ Terminal and respiratory bronchioles extend into peribronchiolar regions, alveolar ducts and alveolar space.	▪ Patchy lesions with peribronchiolar distribution.
LCH	▪ Increased number of CD1 Langerhans cells in the bronchiolar wall >50%; ▪ Granulomatous inflammation; ▪ Stellate fibrosis with cyst formation (destruction of the airway walls by Langerhans' cell granuloma.	▪ Around or adjacent to small airways.	
HP	▪ Poorly formed peribronchiolar granuloma; ▪ Patchy mononuclear cell infiltration of the alveolar walls.	▪ Located near respiratory or terminal bronchioles and alveolar walls.	

RB: Respiratory bronchiolitis; RB-ILD: Respiratory bronchiolitis-associated interstitial lung disease; DIP: Desquamative interstitial pneumonia; COP: Cryptogenic organizing pneumonia; LCH: Langerhans cell histiocytosis; HP: hypersensitivity pneumonitis; MFs: Macrophages.

Cigarette smoking is the most frequently encountered risk factor for COPD and lung cancer, but it plays an important role in interstitial pulmonary fibrosis [15]. Katzenstein *et al.* documented that a high proportion (60%) of smoker patients without any clinical sign of interstitial lung disease presented severe interstitial fibrosis: three cases were classified as asbestosis, usual interstitial pneumonia and LCH, and the remaining cases were considered as smoking-related interstitial fibrosis. These lesions were different degrees of alveolar septal widening by collagen deposition, respiratory bronchiolitis and emphysema [16].

Since 2013, smoking-related interstitial lung diseases have been a distinct group of the international classification of IIPs comprising two diseases with overlapping histopatho-logical manifestation: RB-ILD and DIP [2]. The specific pathological feature is RB, characterized by tan-pigmented macrophages (smokers' macrophages) present in the respiratory bronchioles [4]. If the RB is very common in smokers, RB-ILD is rare (7%) [17].

From the histopathology point of view, it is important to take into consideration that not always it is possible to differentiate between RB, RB-ILD, and DIP, knowing that these could share the same features [3, 11, 17]. Some authors consider that the lesions reflect the same disease in a different stage of evolution [18]. The degree of fibrosis (more prominent in RB-ILD), HRCT findings, clinical symptoms and pulmonary function tests improve positive diagnosis.

Another differential diagnostic challenge is the association between CPFE and NSIP [19]. Exposure history, lesions pattern on HRCT (presence of diffuse bronchial wall thickening and patchy dispose of ground-glass opacity are more specific for RB-ILD), BAL findings may help in differentiating these entities [20]. Ground glass opacities with upper lobes predominance are the most frequent findings on HRCT in RB-ILD [21]. Also, pulmo-nary function tests show a mixed obstructive-restrictive pattern, usually with a mild to moderate reduction in DL_{CO} [4]. Some patients have normal function tests [22].

Some studies show variable prognosis in patients who quit smoking, survival higher than seven years being reported in 75% of patients in one study [23]. Like other few cases published in the literature, our patient has a good evolution after smoking cessation. However, clinical and functional deterioration was observed in some patients despite the smoking cessation or treatment [17, 19]. Corticosteroids and immunosuppressive treatment are indicated in cases with lung function deterioration, but their efficacy is not well demonstrated. In one study, the extent of ground glass and bronchial wall thickening on HRCT decreased in 43% of patients after corticosteroids and smoking cessation [21]. The relapses were also cited after corticosteroid cessation or smoking relapse [24].

⌕ Conclusions

RB-ILD is an IIP related to cigarette smoking with an unknown incidence and with an unclear pathogenic mechanism. We described a clinical case of a young smoker with non-specific clinical features, with a radiological pattern of IIP and a moderate impairment of the DL_{CO},

in which BAL was non-diagnostic, and the lung biopsy was needed to confirm the diagnosis of RB-ILD. Smoking cessation is the main recommendation, and corticosteroid treatment is indicated only in patients with proven dete-rioration of the lung function.

Conflict of interests

The authors declare that they have no conflict of interests.

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