CASE REPORTS

Desquamative Interstitial Pneumonia and Respiratory Bronchiolitis-Associated Interstitial Lung Disease: Data From the Spanish Patient Registry

Adolfo Baloira,[a] Antoni Xaubet,[b] Eulogio Rodríguez Becerra,[c] Ana Dolores Romero,[d] Álvaro Casanova,[e] and Julio Ancochea[e]

[a]Servicio de Neumología, Complejo Hospitalario, Pontevedra, Spain
[b]Servicio de Neumología, Hospital Clínic, CIBER de Enfermedades Respiratorias, Barcelona, Spain
[c]Unidad Médico Quirúrgica, Hospital Virgen del Rocío, Sevilla, Spain
[d]Servicio de Neumología, Hospital Virgen de las Nieves, Granada, Spain
[e]Servicio de Neumología, Hospital de la Princesa, Madrid, Spain

Among the idiopathic interstitial lung diseases, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP) make up a subgroup of rare diseases that are clearly smoking related. Few large case series have been published.

We describe 19 cases registered in Spain: 12 patients with DIP and 7 with RB-ILD. Clinical and radiologic features are described along with clinical course, treatments applied, and outcomes. With the exception of 2 patients with DIP, all were smokers or ex-smokers. Cough and dyspnea were the most common symptoms at onset in both diseases. The most frequent radiologic findings were ground-glass opacity in DIP and pulmonary nodules in BR-ILD. Most patients were treated with corticosteroids. Outcomes were good in general; only 1 patient, with DIP, died.

Key words: *Desquamative interstitial pneumonia. Respiratory bronchiolitis-associated interstitial lung disease. Smoking.*

Neumonía intersticial descamativa y bronquiolitis respiratoria asociada a enfermedad pulmonar intersticial: datos del registro español

Dentro de las neumopatías intersticiales idiopáticas, la bronquiolitis respiratoria asociada a enfermedad pulmonar intersticial (BR-EPI) y la neumonía intersticial descamativa (NID) forman un subgrupo de enfermedades raras que comparten una relación clara con el hábito tabáquico. Se han publicado pocas series con un número importante de pacientes.

En este trabajo se describen las características de 19 casos (12 con NID y 7 con BR-EPI) recogidos en nuestro país. Se detallan las características clínicas, radiológicas y evolutivas, incluidos los tratamientos empleados y sus resultados. Excepto 2 pacientes con NID, todos eran o habían sido fumadores. Tos y disnea fueron los síntomas de inicio más frecuentes, sin diferencias entre las 2 enfermedades. La alteración radiológica predominante en la NID fue el patrón en vidrio deslustrado, y en la BR-EPI, la presencia de nódulos pulmonares. La mayor parte de los pacientes recibieron tratamiento con esteroides. El pronóstico en general fue bueno, y falleció únicamente un paciente con NID.

Palabras clave: *Neumonía intersticial descamativa. Bronquiolitis respiratoria asociada a enfermedad pulmonar intersticial. Tabaquismo.*

Introduction

In 1965, Liebow and coworkers[1] described 18 patients with an interstitial disease they considered to be clearly distinguishable from usual interstitial pneumonia. Because the alveoli of these patients characteristically contained cells that were initially believed to be type-II pneumocytes, their disease was termed desquamative interstitial pneumonia (DIP). The following year, Gaensler and colleagues[2] reported on their observations while following 12 patients with DIP. In the 1970s, the "desquamative" cells were found to be macrophages,[3] but the name DIP has nevertheless remained with us to this day. Then, in 1987, Myers et al[4] described 6 heavy smokers with interstitial lung disease evident on radiographs. Histology showed an abundance of macrophages in the terminal bronchioles of those patients as well as thickening of alveolar septa. This disease was termed respiratory

Correspondence: Dr A. Baloira
Servicio Neumología, Hospital Montecelo
Mourente Montecelo, s/n
36071 Pontevedra, Spain
E-mail: adolfobaloira@sogapar.org

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bronchiolitis-associated interstitial lung disease (RB-ILD). The observations of Myers and coworkers were later confirmed in several small case series.[5] DIP and RB-ILD—thought to be different types of responses to tobacco smoke[6,7]—are both extremely rare, though exact figures are difficult to obtain for RB-ILD.[8] A large series recently provide a wealth of clinical data on RB-ILD,[9] but no conclusions could be drawn regarding incidence. DIP, meanwhile, is estimated to account for around 3% of all interstitial lung diseases. However, among the 9 points of uncertainty about DIP listed in the 2002 consensus statement of the American Thoracic Society and the European Respiratory Society,[10] the first concerned the incidence and prevalence of the disease. In an attempt to provide additional data on this rare group of diseases, we aimed to create a register of cases diagnosed in Spain and analyze the characteristics observed.

Case Descriptions

As many DIP cases as possible were identified and a data collection sheet was used to record information on relevant medications taken or possible environmental exposure; smoking history; concomitant diseases; onset symptoms; the results of physical examination; date of diagnosis (by open lung or video-assisted thoracoscopic biopsy); results of laboratory tests, including autoimmune assays; radiology, according to 7 predefined patterns evident on high resolution computed tomography (CT); results of studying bronchoalveolar lavage fluid, transbronchial biopsy or lung biopsy; treatment; duration of follow-up; clinical, radiologic, analytic and functional outcome; changes in therapy; and in case of death, the cause and time elapsed since diagnosis. Only patients with a lung biopsy indicative of DIP or RB-ILD were included.

The study was descriptive and small, placing evident constraints on the statistical analysis. Qualitative variables have been expressed as means (SD), and comparisons between DIP and RB-ILD patients were performed using the Wilcoxon test for continuous variables and the Fisher exact test for categorical variables.

TABLE 1
Patient Characteristics[a]

	DIP (n = 12)	RB-ILD (n = 7)
Sex, female/male	0/12	2/5
Age at diagnosis, y	50 (16)	46 (14)
Smoking		
Current smoker	4	5
Ex-smoker	6	2
Never smoker	2	0
Pack-years	25 (3-80)	32 (12-45)
Symptoms		
Chance finding	1	0
Cough	9	3
Dyspnea	7	6
Crackles	11	3
Clubbing	7	0
Follow-up,[b] mo	29 (12)	32 (16)
Decline		
Clinical	4	0
Functional	2	2
Death	1	0

Abbreviations: DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease.
[a]Data are expressed as number of patients, mean (SD), or mean (range).
[b]Information on clinical follow-up was available for 18 patients (11 with DIP). Respiratory function information was available for 14 patients (9 with DIP). See text for further details.

TABLE 2
Findings on Computed Tomography of the Thorax[a]

	DIP (n = 11)	RB-ILD (n = 7)
Ground-glass opacity[b]	11	3
Nodules[b]	0	3
Alveolar consolidation	2	1
Traction bronchiectasis	3	2
Honeycombing	5	4

Abbreviations: DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease.
[a]No computed tomography scans were available for 1 patient with DIP.
[b]Statistically significant difference.

Clinical Characteristics

The registry held information on 19 patients (12 with DIP and 7 with RB-ILD) whose characteristics are shown in Table 1. The patients with DIP (mean age, 50 [16] years) were slightly older than the patients with RB-ILD (mean age, 46 [14] years). Only 2 patients with DIP had no history of smoking. Patients with RB-ILD had smoked slightly more, with a mean of 32 (16) pack-years compared to 25 (25) pack-years for DIP patients. Two patients diagnosed with RB-ILD were infected with the human immunodeficiency virus (HIV) and had been receiving antiretroviral therapy for more than 2 years. One of those HIV-positive patients also had a positive serology for hepatitis C virus. Both patients had been intravenous drug users. One of the patients with DIP was a metalworker. Another, diagnosed with RB-ILD, worked with silicone. The remaining patients had no relevant environmental exposures. Nor had they been treated with drugs that might have harmed the respiratory tract.

The most common symptoms at onset were dyspnea (13 patients) and cough (12 patients). For 1 asymptomatic DIP patient the diagnosis was based on a chance finding. The most common lung sounds were crackles (14 patients). Only 1 patient, with DIP, had normal lung sounds. Seven of the 12 patients with DIP showed signs of clubbing; no clubbing was seen in the group with RB-ILD.

Radiologic Findings

In 3 cases (2 with DIP and 1 with RB-ILD), the chest radiograph showed no abnormalities. All others displayed some type of lesion. A diffuse interstitial pattern, seen in 7 cases, was the most frequently observed. Alveolar and interstitial opacities were visible on images for 5 patients; for 2 the pattern was only alveolar. Imaging information was unavailable for 1 patient with RB-ILD. Ground-glass opacity, the most common CT pattern observed, was evident in the scans of 13 patients (all but 1 of the patients with DIP and 3 of the patients with RB-ILD, P=.047). Three patients with RB-ILD had pulmonary nodules (Figure 1), a finding not reported for any patient with DIP (P=.043). Nine patients (5 with DIP and 4 with RB-ILD) had evidence of diffuse interstitial disease. Honeycombing was seen in the scans of 1 patient with RB-ILD. Traction bronchiectases were visible in the images of 3 patients with DIP and 2 with RB-ILD (Figure 2). CT images could not be obtained for 1 patient with DIP (Table 2).

Lung Function Test Findings

No significant between-group differences were found in respiratory function. Tests (available for 17 patients, Table 3) showed a mixed pattern with slightly reduced lung volumes and

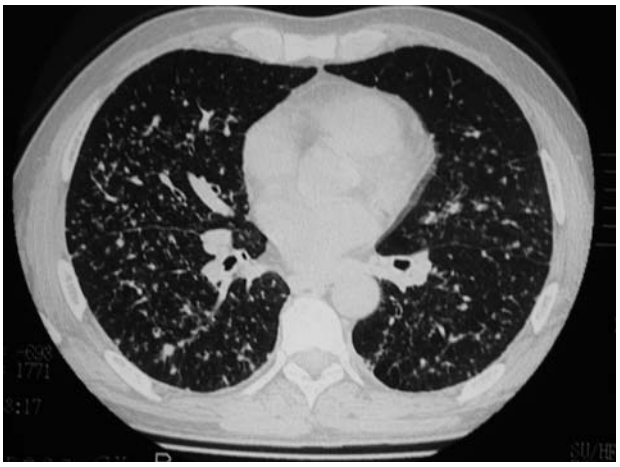

Figure 1. High-resolution computed tomography scan of a 51-year-old man with respiratory bronchiolitis-associated interstitial lung disease who was a smoker at the time of diagnosis (35 pack-years). The scan reveals signs of diffuse interstitial disease. Micronodular lesions predominate. Nodules with different degrees of attenuation can be seen.

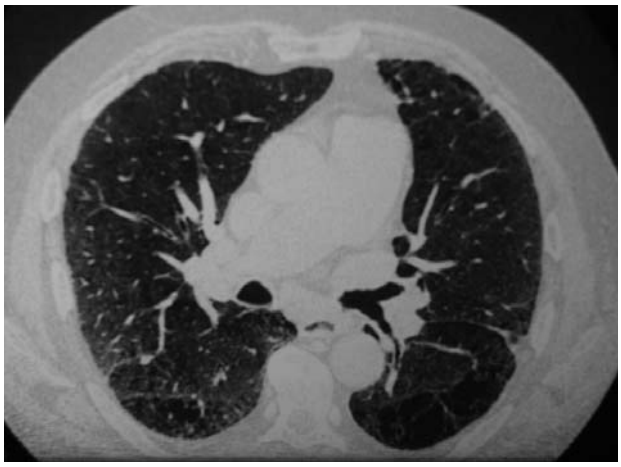

Figure 2. High-resolution computed tomography scan of a 59-year-old man who was a heavy smoker. The scan shows areas of paraseptal and central emphysema in the upper halves of both lungs. Signs of interstitial disease are evident, with areas of ground-glass opacity and traction bronchiectases. Biopsy findings supported a diagnosis of desquamative interstitial pneumonia.

more marked loss of carbon monoxide diffusing capacity. Only 4 patients (2 in each group) had normal volumes. Carbon monoxide diffusion was reduced in all but 2 patients (1 in each group). The reduction was more marked in patients with DIP ($P<.02$). In general gas exchange was more seriously impaired in patients with DIP, and 4 DIP patients were in respiratory failure when diagnosed.

Bronchoalveolar Lavage and Transbronchial Biopsy

Bronchoscopy was performed on 15 patients, 12 of whom had not been diagnosed. Transbronchial biopsy findings suggested a diagnosis of DIP in 3 patients. DIP was later confirmed by open lung biopsy. Findings in bronchoalveolar lavage fluid were available for 13 patients (9 with DIP). Macrophages (which accounted for 55% to 98% of the total number of cells collected) predominated in most cases in which hyperpigmentation was present. The percentages of lymphocytes and neutrophils varied. The percentage of eosinophils was greater than 10% for 2 patients with DIP and 1 with RB-ILD. The distribution of cell types was similar in the 2 diseases.

Treatment

Initial treatment was with oral corticosteroids for 9 patients with DIP and 4 with RB-ILD. Prednisone and azathioprine were prescribed for 2 other patients with DIP, both of whom had marked interstitial disease. One patient was treated only with azathioprine.

TABLE 3
Lung Function at the Time of Diagnosis[a]

	DIP (n = 12)	RB-ILD (n = 7)	*P*
FVC	77 (25)	79 (27)	NS
FEV_1	71 (19)	73 (18)	NS
TLC	76 (24)	79 (21)	NS
DLCO	49 (23)	69 (10)	<.02
PaO_2, mm Hg	63 (18)	78 (13)	NS

Abbreviations: DIP, desquamative interstitial pneumonia; DLCO, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; TLC, total lung capacity.
[a]Mean (SD) lung function results are expressed as percentages of reference values.

No patient with RB-ILD received immunosuppressant therapy. The only therapeutic measure suggested to 3 patients was to quit smoking.

Outcome

The mean duration of follow-up was 23 months (range, 1-69 months). Only 4 patients with DIP showed signs of worsening. One died of respiratory failure 40 months after diagnosis. CT images were available for the final period of follow-up for 13 patients (8 with DIP). No changes were evident in 5 patients (3 with RB-ILD and 2 with DIP), and signs of disease had completely disappeared in 1 patient with DIP. Three patients improved. The extension of ground-glass opacity increased in 2 patients in spite of treatment with corticosteroids. A certain degree of honeycombing was present in 1 of these patients. Lesions progressed in only 1 patient with RB-ILD. Follow-up lung function test results were available for 14 patients (9 with DIP). Eight patients (6 with DIP) improved. Four (2 in each group) had reduced lung function. One of these patients (with DIP) had continued to smoke heavily, and another (with RB-ILD) was a smoker of 50 pack-years who also had signs of emphysema on CT; those factors may have influenced the decline in lung function. There was no clear correlation between changes in lung function and CT findings (Figures 1 and 2).

Discussion

DIP and RB-ILD are both rare diseases which, along with Langerhans cell histiocytosis, can be included among smoking-related interstitial diseases. Connective tissue disease has been reported in some cases of DIP[5] and in at least 1 case of RB-ILD—a nonsmoker who worked as a welder—in the series of Moon et al.[11] A surprising association was noted in a male smoker who developed DIP after he acquired a tattoo on his back; that case was fatal.[12] Only 2 patients with DIP in our series had never smoked. One of them had been a metalworker. The inclusion of 2 HIV-infected patients in the group with RB-ILD is noteworthy, as none were HIV-positive in the 2 largest series in the literature.[6,9] Heavy smoking was

probably the causative factor, however, and we cannot be sure that the virus played any role. One group has reported the case of a patient who had never smoked; that patient had received a kidney transplant and was coinfected by *Aspergillus fumigatus* and the cytomegalovirus.[13] Age at the time of diagnosis was very similar in our series and others in the literature, though our patients with DIP were slightly older. The median age of onset was in the fifth decade of life.

The most frequent symptoms at onset in both diseases were cough and dyspnea. The latter is usually mentioned in the literature on both diseases, and prevalence rates are as high as 94% in the case of RB-ILD and 87% in cases of DIP.[8] Our patients with DIP most often complained of cough (75%). Another point on which our series differs from others is in the slightly higher rate of clubbing (58%). None of the patients with RB-ILD had clubbing, although 42% of the patients of Ryu et al[8] and 69% of the patients of Portnoy et al[9] had this sign.

The radiologic finding that was most common was the presence of ground-glass opacity. Although that pattern was seen in both diseases, it was most characteristic of patients with DIP. The absence of ground-glass opacity on any of the simple radiographs, however, is an indication of the importance of performing CT scans of the chest. The chest x-ray detected no abnormalities in 3 cases (17%) in our series, consistent with reports from other authors.[5,8] A ground-glass opacity pattern is not uncommon in smokers. A study in healthy persons found that 20% of those who smoked had lesions evident on CT but that this was not the case for those who never smoked.[14] Radiologic changes were variable and the outcome was generally better for DIP patients, although lesions fully resolved for only 1 of the 8 patients for whom follow-up images were available. Recently, a small study of Japanese patients found that quitting smoking was correlated with improvements in radiologic findings.[15] Because of the size of our cohort we were unable to extract similar data, but it does not seem to us that quitting smoking had a clear effect on radiologic outcome, an opinion that is shared by other authors.[3,9,16] Accumulated smoking dose does appear to be related to the extension of lesions observed on CT scans at the moment of diagnosis.[17] One of our patients with progression of respiratory function impairment on follow-up had centroacinar emphysema evident on CT. We had initially assumed that the micronodules seen in bronchiolitis were a preliminary step toward emphysema, as this has been shown to occur at least in some patients.[18] Many have disagreed, however, suggesting that progression most likely leads to fibrosis.[17,19] In 13 of our patients who underwent bronchoalveolar lavage, we saw marked elevation in hyperpigmented macrophages, as is usual in smokers. However, there are no data that are specific enough to help rule out other interstitial diseases. Nor are there factors that distinguish between DIP and RB-ILD patients.

It is difficult to draw conclusions regarding treatment. Most patients were treated, usually with oral corticosteroids. Clear benefits were seen in some DIP cases, but improvement was much less evident among RB-ILD patients. Improvement could be demonstrated on CT for at least half the patients with DIP, although disease progression was observed in 2 cases. It is noteworthy that only 1 patient had a normal CT scan at the end of follow-up. We found there was considerable discrepancy between the patients' subjective impressions of their condition and data from lung function tests and imaging studies. Of the 16 patients who were followed for at least 9 months in our series, 12 (75%), including all those with RB-ILD, reported that symptoms had improved, even though the results of lung function tests had improved in only 7 (45%). Our findings differ from those of Ryu et al,[8] who observed a higher percentage of patients with objective improvements (33% of those with DIP and 64% of those with RB-ILD) than subjective improvement (24% and 55%, respectively). The behavior of both diseases was generally benign in terms of outcome in our series. Only 1 patient (with DIP) died, whereas 5 deaths occurred in the series reported by Ryu and coworkers. The 10-year survival rate has been estimated to be approximately 70%.[7] None of the patients with RB-ILD died during the follow-up period, underscoring the benign nature of that disease. A 7-year survival of at least 75% has been estimated.[9]

This series of 19 patients evidently does not allow us to come to conclusions about the incidence of idiopathic interstitial lung disease in Spain. Our findings are fairly similar to those of other series, but there are certain differences. It seems clear that smoking is an important etiologic factor, although recurrence of DIP in the transplanted lung[20] obliges us to consider the possibility of a systemic pathogenic mechanism in some cases. The clinical course is usually benign, particularly for RB-ILD, and even though the effect of quitting smoking is not certain, patients with these diseases should be strongly urged to quit. It seems unlikely that RB-ILD develops into DIP. Treatment with corticosteroids is usually somewhat effective, but chest CT lesions remain in many cases and some patients may die due to disease progression. It would be useful to study larger series, as most published studies are small and usually include patients being treated in referral hospitals, a situation which introduces considerable bias.

Appendix

The following persons also contributed cases to this series: Isabel Mir (Hospital Sant Llàtzer, Palma de Mallorca) and Estrella Fernández Fabrellas (Hospital Dr Peset, Valencia).

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