Desquamative Interstitial Pneumonia and Respiratory Bronchiolitis-Associated Interstitial Lung Disease*

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Background: **Desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) are uncommon forms of interstitial lung disease and have been incompletely characterized.**
Study objectives: **To further characterize the clinical features and course of subjects with DIP and RB-ILD.**
Design: **Retrospective study.**
Setting: **Tertiary care, referral medical center.**
Patients: **Twenty-three subjects with DIP and 12 subjects with RB-ILD seen over a 12-year period between 1990 and 2001.**
Interventions: **None.**
Results: **The study population included 19 men (54%) and 16 women (46%). The mean (± SD) age at diagnosis was 46 ± 10 and 43 ± 7 years, respectively, for patients with DIP and RB-ILD. All subjects were either current or previous smokers except for three subjects with DIP. The diagnosis was confirmed in all cases by surgical lung biopsy. Bronchoscopy with transbronchial lung biopsy had been performed in 12 patients and was nondiagnostic in all. The most common pulmonary function abnormality was a reduced diffusing capacity of the lung for carbon monoxide. A CT scan of the chest revealed ground-glass opacities bilaterally in most patients who had DIP and RB-ILD. No differences were observed between subjects with DIP and RB-ILD with respect to clinical features, radiologic findings, or pulmonary function test results. The clinical course was characterized by relative stability in the majority of patients in both groups and a partial response to corticosteroid therapy. Five deaths were observed, including three resulting from progressive diffuse lung disease, all in subjects with DIP.**
Conclusions: **We concluded that DIP and RB-ILD are chronic disease processes that in most patients are related to smoking. Persistent abnormalities can be seen on pulmonary function testing and radiologic studies despite smoking cessation and corticosteroid therapy. Corticosteroid therapy appeared to be associated with modest clinical benefit but usually not with resolution of disease. Progressive disease with eventual death can occur in subjects with DIP, especially with continued cigarette smoking.** ***(CHEST 2005; 127:178–184)***

Key words: desquamative interstitial pneumonia; interstitial lung disease; respiratory bronchiolitis

Abbreviations: ATS = American Thoracic Society; DIP = desquamative interstitial pneumonia; DLCO = diffusing capacity of the lung for carbon monoxide; ERS = European Respiratory Society; HRCT = high-resolution CT; ILD = interstitial lung disease; RB = respiratory bronchiolitis; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease

Desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) are associated with cigarette smoking and represent two of seven entities that are currently included under the category of *idiopathic interstitial pneumonias*.[1–8] These terms, *DIP* and *RB-ILD*, have been used to describe both his-

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topathologic patterns and clinicopathologic entities that incorporate clinicoradiologic as well as histopathologic features. A limited number of case series[4,8] have been reported, and some aspects of these disorders as well as their relationship to other forms of idiopathic interstitial pneumonias remain to be clarified.

In an effort to further characterize these two disorders, we identified 35 patients with clinicoradiologic evidence of interstitial lung disease (ILD) and DIP or RB-ILD patterns identified on lung biopsy specimens. We examined the clinical and radiologic presentation of these subjects, as well as their clinical course.

Materials and Methods

We conducted a computer-assisted search of the Mayo Clinic database to identify cases of DIP and RB-ILD that were seen at our institution over a 12-year period between January 1, 1990, and December 31, 2001. All lung biopsy specimens were reviewed to confirm the histopathologic pattern of either DIP or RB-ILD.

RB-ILD was defined by the presence of clinical and radiologic evidence of ILD occurring in a patient with histologically proven respiratory bronchiolitis (RB) seen on a surgical lung biopsy specimen. The histologic diagnosis of RB required the presence of yellow-brown-pigmented macrophages in the lumens of respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces without significant associated interstitial pneumonia. Similarly, DIP was diagnosed in patients with clinical and radiologic evidence of ILD, and a histologic pattern of DIP on surgical lung biopsy specimens. Several investigators[4,5,9,10] have highlighted the histologic overlap between RB and DIP. For the purposes of our study, DIP was defined by the presence of pigmented macrophages diffusely involving alveolar spaces in at least one low-magnification field (×40) without a bronchiolocentric distribution and accompanied by diffuse alveolar septal thickening due to alveolar septal inflammation with or without fibrosis. Patients with incidental RB or DIP noted on their lung specimen obtained for an unrelated purpose (*eg*, lung cancer resection) were excluded from this study.

Medical records were examined in detail to gather clinical, radiologic, and pulmonary function data at presentation. Follow-up data regarding their clinical course, results of subsequent radiologic and pulmonary function studies, response to treatment, and clinical outcome also were extracted. The eventual clinical outcome was assessed at the time of the last available follow-up visit and was categorized as improved, stable, or worsened using the criteria published in a American Thoracic Society (ATS)/European Respiratory Society (ERS) statement.[11] These criteria include the assessment of changes in respiratory symptoms, radiologic findings, and pulmonary function measurements (*ie*, total lung capacity, vital capacity, diffusing capacity of the lung for carbon monoxide [DLCO], and oxygen saturation or Pao_2).[11]

Spirometry and measurements of lung volumes and DLCO were performed in our laboratory using standard techniques.[12] Pulmonary function data included plethysmographically determined total lung capacity, FVC, FEV_1, FEV_1/FVC ratio, and DLCO.

This study was approved by the Mayo Foundation institutional review board. Patients who did not authorize the use of their medical records for research were excluded from this study (two patients).

Statistical Analysis

Patient characteristics were compared between groups using the two-sample rank sum test for continuous variables and an exact test for categoric variables. The log-rank test was used to compare the survival of groups of patients. In all cases, two-tailed p values of < 0.05 were considered to be statistically significant.

Results

We identified 23 patients with DIP and 12 patients with RB-ILD who were seen at our institution over a 12-year period between 1990 and 2001. The mean (± SD) duration of follow-up from the initial visit at our medical center with diagnosis was 19.6 ± 29.5 and 11.8 ± 16.5 months, respectively, for subjects with DIP and RB-ILD. The mean duration of follow-up from the time of surgical biopsy was 37.7 ± 44.6 and 17.3 ± 15.4 months, respectively, for subjects with DIP and RB-ILD. Bronchoscopy with transbronchial lung biopsy was performed in 12 patients (DIP, 7 patients; RB-ILD, 5 patients) and yielded nondiagnostic results in all.

Nineteen subjects (54%) were men and 16 subjects (46%) were women (Table 1). The mean age at diagnosis was 46 ± 10 and 43 ± 7 years, respectively, for patients with DIP and RB-ILD. Thirty-two patients (91%) were either current or past smokers. Three subjects with DIP were nonsmokers, and no environmental exposure or underlying disease was identified in these three subjects. The most common symptoms at presentation were dyspnea (83% of all patients) followed by cough (46% of all patients). There were no significant differences when comparing the DIP and RB-ILD groups with respect to gender, age, smoking status, smoking history, or presenting symptoms ($p \geq 0.183$).

Chest radiographs demonstrated the presence of bilateral interstitial infiltrates in the majority of patients, some of whom had DIP and some of whom had RB-ILD. However, two subjects in each group had no parenchymal infiltrates noted on the initial chest radiographs. Of 26 patients who underwent high-resolution CT (HRCT) scanning of the chest at the time of their initial evaluation, 23 patients (88%) had ground-glass opacities as the predominant finding, including 83% of subjects with DIP and 100% of those with RB-ILD. Reticular and consolidative opacities were uncommon (Table 1). Honeycombing, with minimal peripheral involvement, was noted in only one subject with DIP. No significant differences were noted in the radiologic findings (chest radiography or CT scan pattern at presentation for

Table 1—*Epidemiologic, Clinical, Radiologic, and Pulmonary Function Features for Patients With DIP and RB-ILD

Characteristic	DIP (n = 23)	RB-ILD (n = 12)
Male sex	11 (48)	8 (67)
Age, yr		
Mean ± SD	46 ± 10	43 ± 7
Median	44	44
Range	26–69	33–54
Smoking status		
Current	18 (78)	10 (83)
Previous	2 (8)	2 (17)
None	3 (13)	0 (0)
Smoking history, pack-yr		
Mean ± SD	38 ± 21	29 ± 21
Median	31	25
Range	10–90	3–75
Presenting symptoms		
None	1 (4)	1 (8)
Dyspnea	20 (87)	9 (75)
Cough	10 (43)	6 (50)
Chest pain	4 (17)	1 (8)
Physical signs		
Inspiratory crackles	13 (57)	5 (42)
Digital clubbing	6 (26)	3 (25)
Chest radiographic pattern†		
Bilateral interstitial	18 (82)	6 (60)
Unilateral interstitial	1 (5)	1 (10)
Patchy ground glass	1 (5)	1 (10)
No infiltrates	2 (9)	2 (20)
Predominant CT scan pattern‡		
Bilateral ground-glass opacities	15 (83)	8 (100)
Bilateral reticular densities	3 (17)	1 (13)
Patchy consolidation	1 (6)	0 (0)
Pulmonary function§		
Restrictive	6 (30)	5 (50)
Obstructive	3 (15)	3 (30)
Low diffusion capacity only	7 (35)	1 (10)
Normal	4 (20)	1 (10)

*Values given as No. (%), unless otherwise indicated.
†Chest radiograph was not available in one DIP case and two RB-ILD cases.
‡CT chest was not available in five DIP and four RB-ILD cases.
§Pulmonary function results within 6 months of diagnosis was not available in three DIP cases and two RB-ILD cases.

patients with DIP compared to RB-ILD, $p \geq 0.454$). Only three patients (DIP, two patients; RB-ILD, one patient) had a repeat CT scan available after ≥ 2 years of follow-up, and all three demonstrated a relatively stable appearance of mostly ground-glass opacities with no honeycombing seen (Fig 1).

Thirty patients had pulmonary function test results available from testing that had been performed within 6 months of the initial diagnosis (Table 1). Eleven patients (37%) had restrictive abnormalities found on pulmonary function testing, while 6 patients (20%), 3 from each group, had a predominantly obstructive defect. Overall, 25 patients (83%) had a reduced DLCO, and in 8 of these patients, reduced DLCO was the only pulmonary function abnormality found. Five patients (17%) had normal pulmonary function test results. A summary of pulmonary function values is provided in Table 2. Pulmonary function impairment observed and the values of pulmonary function parameters were similar between groups.

Most patients in both groups underwent a trial of corticosteroid therapy, including 21 patients with DIP (91%) and 11 patients with RB-ILD (92%). Symptomatic improvement (*ie*, improved cough, dyspnea, or both) with prednisone treatment was noted in five patients with DIP (24%) and six patients with RB-ILD (55%). Objective improvement with prednisone treatment, as evidenced by improvement in pulmonary function measurements or parenchymal infiltrates seen on chest radiography

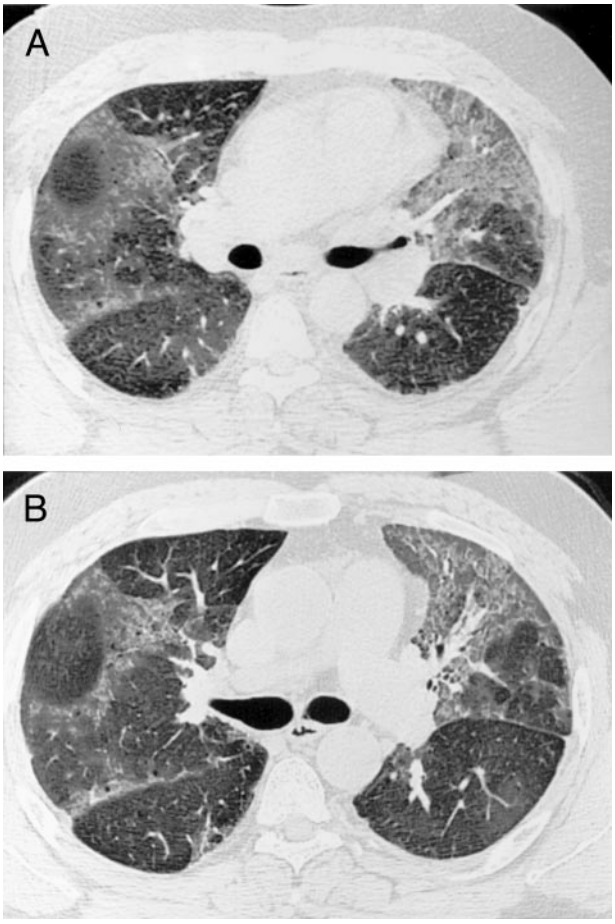

FIGURE 1. A 44-year-old man, a smoker, with DIP. *Top*, *A*: initial HRCT scan demonstrates patchy ground-glass opacities in both lungs. *Bottom*, *B*: HRCT scan performed 24 months later demonstrates persistent ground-glass opacities in both lungs with no substantial changes over the interval and no honeycombing. This patient had successfully quit smoking and had been treated with prednisone at varying dosages over most of the intervening period.

Table 2—*Summary of Pulmonary Function Data at Initial Visit

Parameter	DIP				RB-ILD			
	No.	Median	Mean ± SD	Range	No.	Median	Mean ± SD	Range
Total lung capacity, PP	20	86.0	84.8 ± 18.8	47.0–125.0	9	77.0	77.8 ± 19.2	54.0–111.0
FVC, PP	20	75.5	74.1 ± 16.7	44.0–102.0	10	72.0	72.6 ± 24.9	40.0–113.0
DLCO, PP	19	52.0	52.8 ± 16.7	12.0–86.0	9	62.0	57.3 ± 14.6	34.0–77.0
Oxygen saturation at rest,† %	13	95.0	93.8 ± 3.6	85.0–99.0	7	92.0	91.6 ± 2.8	88.0–95.0
Oxygen saturation with exercise,† %	11	91.0	89.4 ± 5.1	79.0–97.0	7	91.0	88.3 ± 4.9	81.0–93.0

*PP = percent predicted.
†Measures were obtained while patient was breathing room air.

or CT scans was noted in seven patients with DIP (33%) and seven patients with RB-ILD (64%) [Fig 2]. However, these positive responses tended to be transient with a not uncommon worsening of their condition back to baseline values seen (*ie*, DIP, three patients; RB-ILD, two patients) with tapering and discontinuation of prednisone treatment. This regression back to the baseline status occurred even in the absence of smoking (DIP, two patients; RB-ILD, two patients).

Eventual outcome at the end of the follow-up period was assessable using the ATS/ERS criteria[11] in 19 patients with DIP and in all 12 patients with RB-ILD (Table 3). Approximately two thirds of patients in both groups had been assessed as being stable at the time of their last follow-up visit. One subject with DIP (5%) and three subjects with RB-ILD (25%) showed improvement by ATS/ERS criteria. This improvement was associated with prednisone treatment in three of the subjects (two of whom continued to smoke) and smoking cessation alone in the remaining subject who had RB-ILD. Five patients with DIP died (26%) and none of those with RB-ILD died ($p = 0.298$ [log-rank test]). The causes of death for five patients with DIP included respiratory failure (three patients), lung cancer (one patient), and liver cancer (one patient). Deaths from respiratory failure occurred 8, 13, and 40 months, respectively, after the diagnosis of DIP. All three patients were smokers, and at least two of them were known to have continued to smoke. In addition, one patient with DIP and one patient with RB-ILD who worsened by ATS/ERS criteria continued to smoke.

Approximately one third of patients who smoked at the time of diagnosis were successful in quitting. The effect of smoking cessation on the clinical course of these patients was difficult to assess due to the confounding effects of prednisone treatment and incomplete follow-up data. All eight patients who quit smoking (four from each group) were stable or had improved conditions (two RB-ILD subjects) over a follow-up period of 1 to 128 months (median follow-up period, 13.5 months) after undergoing surgical biopsy. Six of these patients had been treated with prednisone (including two RB-ILD patients whose conditions had improved).

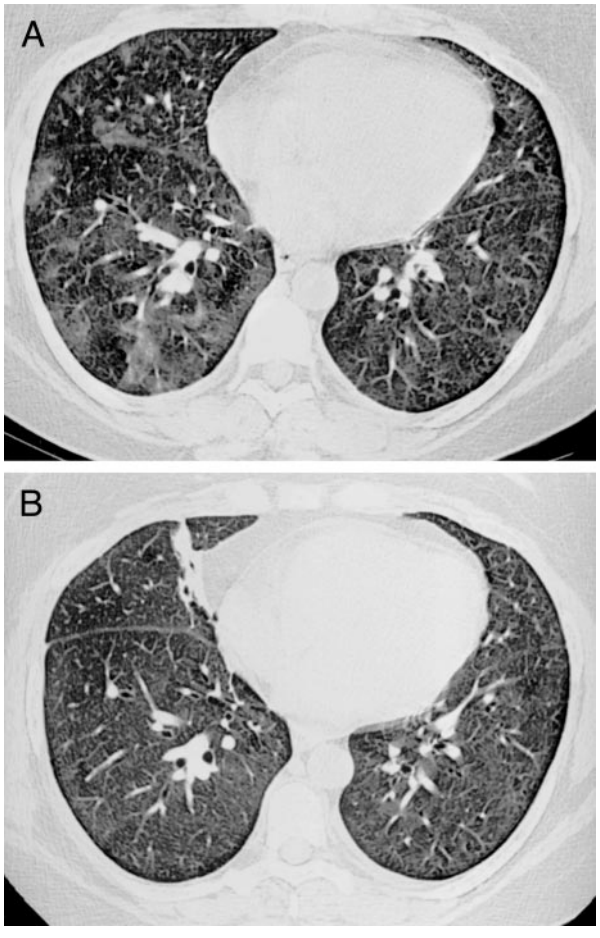

FIGURE 2. A 41-year-old woman, a smoker, with RB-ILD. *Top*, *A*: HRCT scan performed 3 days before she underwent surgical lung biopsy demonstrates patchy ground-glass opacities in both lungs, which are more pronounced on the right side. *Bottom*, *B*: HRCT scan performed 7 weeks later demonstrates substantial improvement in lung infiltrates (postoperative change seen in the right middle lobe). The patient had been treated with prednisone, beginning at 40 mg/d and tapered down to 5 mg/d, along with cessation of smoking.

Table 3—*Treatment and Outcome Data

Characteristic	DIP (n = 23)	RB-ILD (n = 12)
Treatment		
None	2 (9)	1 (8)
Corticosteroids	21 (91)	11 (92)
Smoking cessation†		
Yes	4 (27)	4 (40)
No	11 (73)	6 (60)
Response to corticosteroid therapy		
Subjective improvement	5 (24)	6 (55)
Objective improvement	7 (33)	7 (64)
Final clinical outcome‡		
Improved	1 (5)	3 (25)
Stable	12 (63)	8 (67)
Worsened	1 (5)	1 (8)
Dead	5 (26)	0 (0)

*Values given as No. (%).

†Smoking cessation data are for patients who were current smokers at the index visit (15 DIP subjects and 10 RB-ILD subjects). Smoking cessation status was not known in three patients with DIP who were smokers at entry.

‡Final clinical outcome using the American Thoracic Society criteria could not be assessed in four patients with DIP. The mean length of follow-up after surgical lung biopsy was 9 months for improved patients, 33 months for stable patients, 25 months for worsened patients, and 58 months for dead patients.

Discussion

DIP and RB-ILD are relatively uncommon forms of ILD that are strongly associated with cigarette smoking. Our study confirms the preponderance of smokers among subjects diagnosed with either DIP or RB-ILD. Others have demonstrated a history of smoking in about 90% of patients.[13,14] In never-smokers, DIP is occasionally observed to be associated with other conditions, including connective tissue diseases and drug-induced lung disease.[9] A lesion resembling DIP has been described[14] in infants with mutations in the gene encoding surfactant protein C, and this represents a condition distinctly different from DIP in adults. Rare examples of RB-ILD have occurred in nonsmokers who have experienced other fume exposures.[10] Our cohort included three nonsmokers with DIP in whom we were unable to identify any relevant underlying disease or inhalational exposure.

The clinical and radiologic characteristics of DIP and RB-ILD are not specific. Patients generally present with an insidious onset of dyspnea and cough over a course of weeks or months. In our study population, there were no significant differences in clinical and radiologic presentation when comparing patients with DIP to those with RB-ILD. Most patients in both groups presented with chronic dyspnea and radiologic abnormalities. Inspiratory crackles were present in about one half of patients, and digital clubbing was present in one fourth of those with DIP as well as of those with RB-ILD. These findings are similar to those previously reported by other investigators.[9,10,13,15,16]

As noted in previous studies,[16–21] ground-glass opacities were the predominant finding on chest imaging by CT scan for our patients with DIP and RB-ILD. Ground-glass opacities have been shown to correlate with macrophage accumulation within the alveolar spaces and alveolar ducts.[22] Reticular and consolidative opacities were uncommon. The overlap in radiologic features of DIP and RB-ILD has been described by Heyneman and colleagues,[17] who concluded that RB, RB-ILD, and DIP represent varying degrees of severity of the pulmonary reaction to cigarette smoke. Our results tend to support their conclusion.

Although all of our patients who underwent CT scanning had abnormalities noted, chest radiographs demonstrated no parenchymal infiltrates in several of them. Conventional chest radiograph findings are normal in up to 22% of biopsy-proven cases of DIP.[9,23] The higher sensitivity of CT scanning compared to chest radiography in the detection of ILDs has been well-recognized.[21]

The majority of our patients with DIP and RB-ILD demonstrated a stable clinical course, although radiologic abnormalities tended to persist. Several deaths occurred in patients with DIP from respiratory causes, while no deaths were observed in the RB-ILD group. Carrington and colleagues[13] had previously reported a 27.5% mortality rate in a group of 40 patients with DIP who had been followed up for a mean duration of 9 years. Similarly, Yousem and colleagues[9] noted a 32% mortality rate in their 36 patients with DIP, which is in contrast to no deaths being observed in 18 patients with RB-ILD. Both studies also noted "improvement" in many of their patients, most of whom had received corticosteroid therapy. Specific criteria by which this improvement was judged were not stated in either study. In addition, the durability of this response was not stated. Based on our data and those of previous reports, RB-ILD appears to be associated with a more benign clinical course compared to that of DIP.

There is some evidence to suggest that smoking cessation may suffice as the initial therapeutic maneuver for patients with RB-ILD. None of the patients in our series who quit smoking had progressive disease, but the majority also received corticosteroid therapy. Yousem and colleagues[9] reported that patients with RB-ILD had "resolution of symptoms" after the cessation of smoking. How many of these subjects received corticosteroid therapy is not clear. Six patients with RB-ILD who were initially

reported by Myers and colleagues[2] had minimal or no symptoms on follow-up, although all but one continued to smoke. Three of these patients had been treated with corticosteroid therapy.

It remains unclear whether corticosteroid therapy favorably alters the natural history of DIP and RB-ILD, particularly since the effect of smoking status on the clinical course of patients with these disorders has not been fully delineated. The majority of DIP patients reported by Carrington et al[13] and Yousem et al[9] had been treated with corticosteroid therapy and appeared to experience at least temporary symptomatic improvement. The effect of smoking cessation was not specifically explored in these patients with DIP. Akira and colleagues[20] described an initial decrease in ground-glass opacities in all DIP cases treated with corticosteroid therapy. In three of their cases, however, ground-glass opacities increased again despite continued treatment with "low-dose" corticosteroid therapy. The smoking status of these three patients was not stated.

Although DIP and RB-ILD are smoking–related in most subjects with these disorders, our data suggest that both of these lesions can persist for long periods even after smoking cessation and attempts at corticosteroid therapy. Fraig and colleagues[24] have described the persistence of the RB after many years of smoking abstinence. Several of our patients with DIP and RB-ILD appeared to have a fluctuating course of persistent parenchymal infiltrates and pulmonary function abnormalities, which varied partly with the corticosteroid dose, months to years after smoking cessation. It seems plausible that cigarette smoke antigens or cigarette smoke-induced alterations in the lungs persist for long periods and may continue to provoke a chronic inflammatory reaction.

Due to limited follow-up in many of our patients, we were unable to adequately address the question of whether RB-ILD or DIP can progress to usual interstitial pneumonia. In three of our patients who had a follow-up CT scan after an interval of ≥ 2 years, there was no evidence of progression to honeycombing. Akira and colleagues[20] studied sequential CT scans in eight patients with DIP over a mean follow-up period of 3.2 years and found no evidence of DIP progressing to usual interstitial pneumonitis. Hartman and colleagues[19] noted the development of honeycombing in 1 of their 11 subjects with DIP, which was observed by serial CT scans over a period of 2 to 52 months. Although the number of subjects studied is relatively modest and follow-up data are incomplete, as in our study, on balance, there is little evidence to suggest that DIP progresses to usual interstitial pneumonitis.

We conclude that most patients with DIP or RB-ILD have a relatively stable clinical course, but deaths can occur in those with DIP. Smoking cessation is likely an important component in the management of patients with these smoking-related ILDs, but the influence of smoking on the clinical course of these patients has not been fully delineated. Some of our patients had persistent disease even with smoking cessation and corticosteroid therapy.

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