Desquamative interstitial pneumonia: Risk factors, laboratory and bronchoalveolar lavage findings, radiological and histopathological examination, clinical features, treatment and prognosis (Review)

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Abstract. Desquamative interstitial pneumonia is a type of smoking-associated major idiopathic interstitial pneumonia, which is characterized by accumulation of alveolar macrophages in alveolar lumens and septa and develops secondary to mainly active or passive exposure to cigarette smoke. Desquamative interstitial pneumonia mostly occurs in male smokers in association with non-specific symptoms responsive to steroid therapy and has a better prognosis than usual interstitial pneumonia. To date, no large-scale clinical studies have been performed on desquamative interstitial pneumonia patients. Factors responsible for the scarcity of data on the clinical course of this condition include the retrospective nature of the available information as well as its rare occurrence. Despite this, a general consensus exists as to the nature of its symptoms, association with smoking, age and gender distribution, findings of respiratory function tests, steroid responsivity and mortality. The objective of the present review article was to report on desquamative interstitial pneumonia and to describe its etiology, risk factors and clinical features, as well as the laboratory, bronchoalveolar lavage, radiological and histopathological findings, and the treatment and prognosis of affected patients.

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Contents

1. Introduction

Idiopathic interstitial pneumonias (IIPs) are a group of heterogeneous diseases with unknown etiology, characterized by pulmonary parenchymal distortion caused by varying amounts of fibrosis and inflammation, classified under the heading of diffuse parenchymal lung diseases. While IIPs have been reported since the 19th century, it was in 2002 that the American Thoracic Society (ATS) and the European Respiratory Society (ERS) were the first to define and categorize this condition into seven groups considering clinical, radiological and histopathological findings (Table I) (1), and this classification was revised by the ATS and ERS in 2013 (2). The current classification divides IIPs into three groups: Major IIP, rare IIP and unclassifiable IIP (Table II). Major IIP is further divided into three groups, namely chronic fibrosing IIPs, smoking-associated IIPs and acute or sub-acute IIPs (Table III).

Desquamative interstitial pneumonia (DIP) is a major type of smoking-associated IIP, which is characterized by accumulation of alveolar macrophages in alveolar lumens and septa and develops secondary to mainly active or passive exposure to cigarette smoke. It was first defined in 1965 by Liebow *et al* (3), who described lesions exhibiting extensive alveolar cell proliferation and desquamation associated with mild thickening in distal airways, but not with necrosis (4). The disease was earlier named as such based on the assumption that it was caused by desquamation of alveolar epithelium into the alveoli. Although

the ATS considered 'alveolar macrophage pneumonia' as a more explanatory definition in 2002, this was renounced later (1).

The prevalence of DIP is not exactly known. Global or national epidemiological data are usually for idiopathic pulmonary fibrosis (IPF), which is the most common form of IIPs. No epidemiological data are available for rare forms of IIP, such as DIP; however, a limited number of case-based studies are available (5).

2. Etiology

Despite the more common occurrence in the 4th or 5th decade of life, pediatric cases have also been described in whom surfactant pathology rather than smoking has been implicated. Also smoking-associated pediatric cases have been described (1). The male-to-female ratio is 2:1.

While 100% of respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) cases are linked with cigarette smoking, this figure is 90% for DIP. In addition to smoking, other factors such as systemic disease, infections, environmental/occupational exposure to hazardous agents as well as drugs may be associated with DIP. Although RB-ILD does not occur in children, DIP may rarely be seen in children. In contrast with the significant male predominance (factor 2:1) among DIP cases, there is no marked predominance in RB-ILD. The two conditions generally occur in the 4th to 5th decades of life (6).

With regard to the link between DIP and IPF, a less marked association with cigarette smoking exists for IPF (41-83% of cases). IPF mostly occurs in the middle-aged or elderly population, with a reported male-to-female ratio between 1:1 and 2:1. It may rarely occur during childhood (6).

3. Risk factors

Smoking. The most important widely-recognized factor in the etiology of DIP is the active or passive exposure to cigarette smoke (7). It was reported in 58-91% of smokers (4,6,8-10). Vassollo (11) described smoking as the most important factor in DIP etiology. Craig *et al* (12) assessed histopathologically confirmed interstitial pneumonia cases and detected a smoking history in 12 of 20 DIP cases, a number which they concluded to be significantly higher compared with that among RB cases. Ryu *et al* (13) emphasized smoking in the etiology of DIP and stressed that progressive and fatal cases had a history of heavy smoking.

While an association between smoking and DIP has been fully demonstrated, DIP is also seen in either non-smokers or smoking quitters. This implies the involvement of other etiological risk factors such as environmental or occupational exposure, accompanying diseases or medication use, with or without smoking.

Occupational or environmental exposure to hazardous substances. Regarding occupational exposure to hazardous agents in 8 DIP cases with no smoking history in the study by Craig *et al* (12), diesel or fire smoke, or beryllium exposure had occurred in these cases. In their study on a series of 10 cases, Moon *et al* (14) detected solder smoke and occupational wood dust exposure in two different non-smoker cases.

Another important occupation affecting DIP is the textile industry. Lougheed *et al* (15) reported biopsy-based DIP cases in textile workers employed at cotton/polyester factories. A study performed on 88 textile workers with DIP included five cases with no current smoking status, of which two were non-smokers and the remaining three had a prior smoking history. The authors concluded that a possible factor responsible for DIP development may be aflatoxin inhalation in the workplace. They reported that DIP may develop after exposure to substances including asbestos, talc, graphite, silica and aluminum (15). Liebow and Carrington (16) reported on DIP cases associated with exposure to tungsten cobalt. In a study on the effects of metals on the lung, Nemery (17) suggested that desquamative and giant-cell interstitial pneumonias may occur due to cobalt exposure. Asbestos-associated DIP cases were reported by Corrin and Price (18) in a shipyard worker and by Freed *et al* (19) in a construction worker who was employed for 32 years. Hull and Abraham (20) reported exposure to aluminum welding smoke as a risk factor for DIP. A different type of occupational exposure as a risk factor was pointed out by Nakazawa *et al* (21), who presented a radiologically and histopathologically confirmed DIP case who had been subjected to heavy exposure to occupational waterproof spray. Despite the presence of a smoking history, this occupational factor was regarded to be responsible for the disease. All of these findings, in spite of mostly being derived from case-based studies, demonstrated that environmental or occupational exposure to hazardous substances may have an important role in the etiology of DIP.

Psychotropic substance or medication use and chronic diseases. DIP cases associated with chronic drug or psychotropic drug use have been reported. Carrington *et al* (22) suggested marijuana use as an etiological factor. Pathologically confirmed DIP cases developed secondary to marijuana use and their specimens revealed gold-brown particle-laden macrophages, which was reported to be a distinctive feature of smoking-associated DIP (21). Gill (23) also presented a cannabis-associated case. Certain drugs, including macrolides, sirolimus, nitrofurantoin, sulfasalazine and tocainide were reported to be associated with DIP (21,24). Sirolimus is an immunosuppressive agent whose application is indicated in solid organ transplant patients, amongst whom a large number of pulmonary toxicity cases were reported after sirolimus use. Under circumstances where post-transplant deterioration, dyspnea and hypoxia occur without any evidence of infection, this deterioration may be associated with DIP (25).

DIP was also demonstrated to occur during chronic diseases. A study on 26 DIP cases by Tubbs *et al* (4) reported that 58% of subjects had a history of smoking, and that rheumatologic disorders may have been responsible for the disease in the remaining patients. Ishii *et al* (26), who presented 24 cases where DIP and rheumatologic disease were comorbid, detected positivity of certain markers such as rheumatoid factor and anti-nuclear antibody, and recommended that diagnosis of DIP is established upon histopathological evidence. Kawabata *et al* (27) reported 20 DIP cases emerging during systemic lupus erythematosus.

There are also case presentations showing an association between DIP and infectious diseases. Iskandar *et al* (28)

Table I. Histological and clinical classification of interstitial pneumonia.

Histological pattern	Clinical-radiological-pathological diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Non-specific interstitial pneumonia	Non-specific interstitial pneumonia
Organized Pneumonia	Cryptogenic organized pneumonia
Diffuse alveolar injury	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

Table II. American thoracic Society/European respiratory society classification of IIP from 2013.

IIP classification	Pathology
Major IIP	Idiopathic pulmonary fibrosis
	Idiopathic nonspecific interstitial pneumonia
	Respiratory bronchiolitis interstitial lung disease
	Desquamative interstitial pneumonia
	Cryptogenic organized pneumonia
	Acute interstitial pneumonia
Rare IIP	Idiopathic lymphocytic interstitial pneumonia
	Idiopathic pleuroparenchymal fibroelastosis
Unclassified IIP	-

IIP, idiopathic interstitial pneumonia.

reported on the development of DIP due to immunological response mechanisms during hepatitis C infection. Similarly, Hasegawa *et al* (29) reported DIP in a 72-year-old patient with chronic hepatitis C infection who had no history of active or passive smoking. The condition was thought to occur secondary to an immunological response (29). Cytomegalovirus (CMV) infection was also reported to be involved in the etiology of DIP. Schroten *et al* (30) reported a case of DIP in an 8-month-old infant, developed after CMV infection. Sung *et al* (31) reported a DIP case which occurred during CMV and aspergillus infections in a renal transplant patient.

Rare causes of DIP have also been reported. Arai *et al* (32) presented a DIP case developed after receiving a tattoo, which was attributed to a foreign body reaction. While the most recognized etiological factor is exposure to cigarette smoke, DIP may also result from chronic diseases, medication use and occupational or environmental exposure to various substances, as mentioned above. In particular, DIP should be considered in rheumatologic disease and in transplant patients with new onset of radiological alterations and clinical deterioration in the absence of infection.

4. Diagnosis

Laboratory and bronchoalveolar lavage (BAL) findings. Laboratory tests usually do not reveal any abnormal findings (3). Certain patients were reported to have polycythemia, which was thought to be associated with respiratory insufficiency (3). A study reported elevated lysozyme levels (33). Another study reported increased levels of erythrocyte sedimentation rate, lactate dehydrogenase, immunoglobulin (Ig)G, IgE and interleukin-6 (34).

Slight elevations in eosinophil, neutrophil, lymphocyte and macrophage counts in the BAL fluid have been reported (27,34,35). However, it should be kept in mind that these laboratory and BAL findings are non-specific and to date, no specific sign has been defined.

Radiological finding

Radiological diagnosis of DIP. Chest X-ray findings are non-specific (Fig. 1; patient provided informed consent for inclusion in the present study). While patchy ground-glass opacities located peripherally in lower zones are observed in certain cases, others have normal chest X-rays (1).

Diagnostic radiological findings are rather apparent from thoracic high-resolution computed tomography (HRCT; Fig. 2; patient provided informed consent for inclusion in the present study). An invariable HRCT finding is the presence of a diffuse ground-glass appearance, usually symmetrical and frequently involving the middle and lower zones (6,36,37). While involvement of upper zones is seen in most cases, their predominant involvement is relatively rare. All regions may be affected, although subpleural involvement is most common. Other HRCT findings include irregular lines and traction bronchiectases indicating parenchymal distortion (38). Peripheral microcysts implying dilated bronchioles and alveolar ducts may be seen (39). Honeycomb appearance is not common.

Differential diagnosis. Differential diagnoses should include RB-ILD, hypersensitivity pneumonia and non-specific interstitial pneumonia (NSIP). Certain features outlined below may help to rule out these diagnoses. At times, HRCT findings of RB-ILD may include centrilobular micronodules, ground-glass appearance, linear reticular appearance, atelectasis and emphysema (40-43). Centrilobular nodules and patchy ground-glass appearance tend to be diffuse with no predominance of any zone, unlike the appearance in DIP (44). Emphysema and patchy hypoattenuation are mainly seen in lower zones.

Table III. Classification of major IIP.

Category/clinical-radiological-pathological diagnosis	Morphological pattern
IIP with chronic fibrosis	Usual interstitial pneumonia
Idiopathic pulmonary fibrosis	Non-specific interstitial pneumonia
Idiopathic non-specific interstitial pneumonia	
IIP associated with smoking	Respiratory bronchiolitis
Respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Desquamative interstitial pneumonia	
Acute/sub-acute IIP	Organized pneumonia
Cryptogenic organized pneumonia	Diffuse alveolar injury
Acute interstitial pneumonia	

IIP, idiopathic interstitial pneumonia.

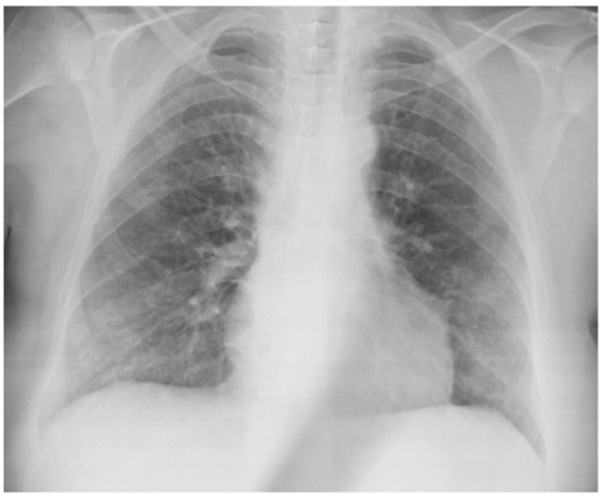

Figure 1. A female patient (age, 55 years) was admitted with chronic cough. Reticular densities were seen on posteroanterior chest X-ray.

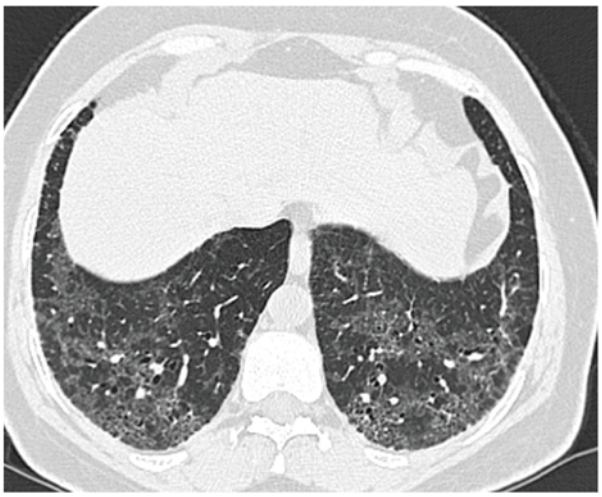

Figure 2. Disorganized ground glass opacity, interlobular septal thickness and minimal honeycomb-like structures were seen on high-resolution computed tomography of the thorax. This is the same patient as presented in Fig. 1.

Radiological findings of NSIP often consists of bilateral, symmetrical and subpleural ground-glass appearance, which is at times superposed by irregularly linear or reticular opacities or traction bronchiectases (39,45,46). Chronic hypersensitivity pneumonia displays at ground-glass appearance, millimetric centrilobular nodules and mosaic perfusion pattern associated with air entrapment in HRCT (47,48). In addition, certain patients may have a honeycomb appearance (49).

Histopathological examination

Histopathological diagnosis of DIP. Due to non-specific laboratory, BAL and radiological findings, surgical biopsy is indicated in cases with suspected IIP with no classical usual interstitial pneumonia (UIP) pattern on HRCT, as recommended by the ATS and ERS (1,50).

When first described, the predominant histological feature of the disease was thought to be desquamation of alveolar epithelial cells, and hence it was named DIP (3). However, electron microscopy images indicated macrophage accumulation in alveoli rather than desquamation of epithelial cells (4). The major characteristic of DIP is proliferation of pneumocytes over the course of alveolar septa and the presence of numerous macrophages, diffusely distributed along with pulmonary acini within alveoli (1,10,51). These macrophages are termed smoker's macrophages, and exhibit eosinophilic cytoplasm and fine granular light brown pigments (10). Fine granular iron may be seen in the cytoplasm of macrophages (52), multinuclear giant cells are frequent (3,5), and eosinophil and lymphoid aggregates may be observed (1,3,4). The alveolar structure is usually preserved despite mild chronic interstitial inflammation. Albeit rare, interstitial fibrosis may be seen. Emphysema is usually observed, but no or minimal honeycomb appearance is present (12).

Differential diagnosis based on histopathology. DIP is listed among smoking-associated IIPs along with RB-ILD and pulmonary Langerhans cell histiocytosis (PLCH) (12,35). RB is a commonly incidental histopathological lesion of smokers,

being mainly asymptomatic (53). RB-ILD is a type of RB characterized by respiratory symptoms as well as radiological and spirometric abnormalities observed in certain smokers. Based on histological findings, of RB could not be differentiated from RB-ILD (54). Although these two clinical entities have distinct diagnostic criteria, histopathological differentiation is compelling (2). The major histological finding in RB-ILD is accumulation of alveolar macrophages in respiratory bronchioles. The most important difference between DIP and RB-ILD is the diffuse and uniform character of this accumulation and lesions in DIP, as compared with the bronchiolocentric character of RB-ILD (40). Unlike in DIP, biopsy of RB-ILD reveals less interstitial fibrosis, and less eosinophil and lymphoid follicles in the interstitium are seen (12). Giant cells are not identified in RB-ILD patients. Since RB-ILD as well as DIP are associated with smoking and smokers with other ILDs have common histopathological features with RB-ILD and DIP, the diagnosis of the latter two conditions may only be established in the absence of signs of ILD (55-58).

NSIP should also be kept in mind for the differential diagnosis of DIP. Varying degrees of fibrosis are seen during histopathological examination of fibrotic NSIP (59). While certain patients have patchy fibrosis due to remodeling of the lung (60), a more diffuse involvement with preservation of the alveolar structure may also be observed. Airspace macrophages are not present. In certain smoking patients, differential diagnosis of DIP and fibrotic NSIP based on radiological or histopathological findings is compelling. It has been suggested that DIP may transform into fibrotic NSIP and certain NSIP cases may be associated with smoking (26), which still remains controversial.

The major histological characteristics of early PLCH, a smoking-associated ILD, is the presence of peribronchial nodules containing Langerhans and inflammatory cells (61). Not grouped among IIPs, airspace enlargement with fibrosis [also termed smoking-associated interstitial fibrosis (SRIF)] and combined pulmonary fibrosis and emphysema (CPFE) are the two conditions histopathologically observed in smokers, and which should be distinguished from DIP. SRIF is a recently described histological pattern (62). It was defined after observation of certain alterations in non-neoplastic pulmonary areas of smoking lung cancer patients who underwent lobectomy (57,62,63). Histopathological observations are incidentally made in these asymptomatic patients. They have mainly sub-pleural emphysematous areas and smoker's macrophages within alveoli. Thickened alveolar septa are seen due to hyperplastic smooth-muscle fibers and eosinophilic collagen structures. While SRIF is an incidentally detected radiological and histopathological condition, CPFE, which is rather a comorbid pathology of IPF, has clinical signs associated with emphysema and interstitial fibrosis (2).

5. Clinical features

DIP, a chronic disease, mostly occurs in male smokers in association with non-specific symptoms responsive to steroid therapy and has a better prognosis than UIP. To date, no large-scale clinical studies have been performed in DIP patients. Factors responsible for the scarcity of data on the clinical course of this condition include the retrospective nature of the available information as well as its rare occurrence. Despite this, a general consensus exists as to the nature of its symptoms, association with smoking, age and gender distribution, findings of respiratory function tests, steroid responsivity and mortality (Table IV).

In their retrospective study, Ryu *et al* (13) examined 33 patients with DIP and 12 patients with RB-ILD. The patient characteristics in these subjects are summarized in Table IV. In that study, a total of 21 DIP patients (91%) received corticosteroids and 4 quit smoking (27%). Improvement was found in 1 patient (5%), while 12 patients (63%) had stable disease, while the disease deteriorated in 1 patient (5%) and 5 patients succumbed to their disease (26%). The causes of death included respiratory failure in 3, lung cancer in 1 and hepatic carcinoma in another.

In the study by Kawabata *et al* (34), a total of 31 DIP patients were followed-up for a duration of 99 months. Their patient characteristics are depicted in Table IV. Patients received pulsed or oral steroids at a daily dose of 15-80 mg, with clinical improvement in 90% of the cases. Seventy patients quit smoking prior to or after treatment. Deaths occurred due to DIP progression, lung cancer, fulminant pulmonary disease after lobectomy and diffuse alveolar disease in one patient each and due to causes not associated with lung disease in another four patients. Lobectomy was performed in three patients due to lung cancer. The 10-year survival rate was 78%.

Craig *et al* (12) reported an average survival of 8.8 years for non-smokers and 7 years for smokers during the follow-up of their patients. Due to the presence of occupational exposure to hazardous substances in their patient group, the authors concluded that it was not possible to definitely determine the causative role of DIP in the development of clinical signs.

Bressieux-Degueldre *et al* (64) reported on a 30-month old female patient who presented with respiratory failure. Physical examination revealed the presence of respiratory rales on auscultation. After a diagnosis of DIP was established, corticosteroid treatment was commenced and the patient was reported to be oxygen-dependent at 2 years of follow-up. DIP represents the most common form of pediatric interstitial lung disease, which has been linked with a genetic defect in surfactant proteins in children. A possible diagnosis of interstitial lung disease should be suspected in children with cough, dyspnea or tachypnea lasting >3 months. Aggressive nutritional support as well as preventive measures against infections are important in the management of children with DIP. Although corticosteroids and immunosuppressive agents are recommended, the prognosis is poor. Lung transplantation represents a therapeutic option during terminal disease.

A 44-year-old patient presenting with shortness of breath, right-sided pleuritic chest pain and orthopnea was described by Behnia and Cummings (65). The patient was found to be sub-febrile and tachycardic, and also had rales in the lower zones of the lung on auscultation. Pulmonary angiography revealed no filling defects. Clinically, the patient was hypotensive and died at 5 days after admission; the diagnosis was established on autopsy.

In addition to those presenting with cough, dyspnea or chest pain, patients presenting with non-specific symptoms such as slightly increased body temperature, myalgia, weight loss, fatigue or respiratory failure have also been reported (66,67).

Table IV. Clinical and functional findings and the disease course in patients with desquamative interstitial pneumonia.

Parameter	Ryu *et al* (13)	Kawabata *et al* (34)	Craig *et al* (12)	Yousem *et al* (10)
N	23	31	20	36
Male sex	11/23 (48)	29/31 (93.5)	12/20 (60)	26/36 (72.2)
Age (years)	46±10	55±13	43	42 (17-67)
Smoking status (current)	18/23 (78)	28/30 (93)	12/20 (60)	33/36 (91.6)
Smoking status (previous)	2 (8)			
Smoking history (pack years)	38±21	52±41		36 (10-71)
Symptoms				
None	1 (4)			5/34 (15)
Dyspnea	20 (87)			29/34 (85)
Cough	10 (43)			26/32 (81)
Sputum				17/33 (52)
Chest pain	4 (17)			
Physical signs				
Inspiratory crackles	13 (57)			5/9 (56)
Digital clubbing	6 (26)			15/36 (42)
Pulmonary function				
Restrictive	6 (30)			
Obstructive	3 (15)			
Low diffusion capacity only	7 (35)			
Normal	4 (20)			
Total lung capacity, PP	84.8±18.8			94 (43-133)
FVC, PP	74.1±16.7	84±23 (VC)		68 (33-124)
DLCO, PP	52.8±16.7			45 (32-78)
Oxygen saturation at rest, %	93.8±3.6			
Oxygen saturation with exercise, %	89.4±5.1			
PaO_2, mmHg		79±11		
Mortality, %	26%	78% (10 years)		8/36 (32)

Values are expressed as the Mean ± standard deviation, n (%), n/total (%), then mean value or mean (range). FVC, forced vital capacity; PP, percent predicted; DLCO, diffusing capacity of the lungs for carbon monoxide; PaO_2, partial pressure of oxygen; VC, vital capacity.

Yousem *et al* (10) assessed 36 DIP patients with chronic symptoms. The clinical characteristics of these patients are summarized in Table IV. In this retrospective evaluation, 14 patients (56%) exhibited improvement during follow-up, while 3 (12%) were stable and 8 patients (32%) died. Comparison between RB-ILD and DIP patients revealed an average diffusion capacity of 62 and 45% in these groups, respectively.

The most common symptoms of DIP include dyspnea and dry cough of insidious onset that may last for weeks or months. In addition, patients with respiratory failure, fever, fatigue and weakness have been reported. Digital clubbing is present in nearly half of the cases (1). Chest pain and weight loss may also occur. Hemoptysis is rare, as are asymptomatic cases. Cyanosis may be seen. DIP may occur in association with connective tissue disorders such as scleroderma, lupus or rheumatoid arthritis, and their symptoms may accompany those of DIP (68).

In patients with DIP, the lung volume is normal or mild restrictive abnormalities may be detected, with moderately reduced diffusing capacity of the lungs for carbon monoxide, which is an indicator of the severity of the underlying disorder. In the assessment of the severity of the functional impairment in DIP, emphysema, which is a frequent co-morbidity, may be a confounding factor (69). Cor pulmonale is rare and hypoxia occurs in the advanced stages of the disease (70).

In each of the two forms of smoking-associated IIPs, DIP and RB-ILD, cough and shortness of breath represent the most common symptoms with an insidious onset (6). Symptoms and clinical features are non-specific in DIP and RB-ILD. The nature of dyspnea in DIP and RB-ILD is slowly progressing exercise dyspnea (69). While rales on auscultation may be heard in each of the two conditions, digital clubbing is more common in DIP. Approximately 60% of DIP patients are found to have rales on auscultation on physical examination. Respiratory function tests reveal a restrictive pattern in DIP, while a mixed defect or normal result may be observed in RB-ILD (6). RB-ILD and DIP respond favorably to steroids with good prognosis, and a complete response may occur.

In IPF, the onset is insidious. Dry cough and shortness of breath comprise the most common symptoms. Almost all

patients have rales on auscultation and digital clubbing is more common (50-70%). Compared to IPF, a less marked effect is observed in respiratory function tests in DIP (6).

6. Treatment and prognosis

Prognosis in DIP is usually favorable and the majority of the patients improve with quitting smoking and corticosteroid therapy. The 10-year survival rate is ~70% (1), with a mortality rate between 6 and 28% (71). Of the untreated patients, almost two thirds have a poor prognosis (6). Despite an insidious onset, the disease may exhibit a rapidly progressive course. Progression to severe fibrosis is rare (70).

Compared to IPF, DIP has a more moderate prognosis with a better response to anti-inflammatory treatment. The mainstay of treatment is quitting smoking, which may, on its own, be sufficient in certain cases (72). Environmental factors and drugs are also implicated in the development of DIP (15,18,73,74). Therefore, termination of any probable environmental risk factors is reasonable. In a study assessing a series of 5 cases of occupational DIP, Lougheed *et al* (15) reported improvement in two cases after moving off the workplace requiring no steroid treatment, and chronic respiratory insufficiency despite steroid treatment in the three remaining cases.

Systemic steroid treatment is recommended in moderately or severely symptomatic patients who progressed despite quitting smoking. While certain patients respond to this treatment based on clinical and radiological findings, others remain stable or the disease progresses (10,75-77). Ryu *et al* (13) followed 23 DIP patients for 12 years and reported symptomatic improvement in 24% of cases that were initiated with steroid treatment. However, they also reported recurrence in certain patients after termination of steroid therapy, even in smoking quitters, where recurrence rates were higher in those resuming smoking or with passive cigarette smoking. It remains to be elucidated whether improvement after steroid initiation depends on steroid treatment or termination of smoking, or results from the natural course of the disease. However, observational studies indicated progression in most of the patients who did not receive any treatment (22). Although no randomized controlled clinical trial proving its efficacy is available, initiation of steroid treatment in all patients with diagnosis of DIP appears to be a reasonable approach with continuance of the treatment upon clinical, radiological and functional improvement and discontinuance in case of no response. Initial steroid treatment consists of 40-60 mg/day for 6 weeks, followed by tapering and cessation of the treatment within 6-9 months (33).

Based on the potential anti-inflammatory effects of macrolides in steroid-refractory cases, Knyazhitskiy *et al* (78) reported rapid and dramatic improvement in all clinical and radiological parameters with clarithromycin treatment in a patient who was refractory to steroid therapy. Similarly, in a case where no response was obtained after initiation of oral steroids, clinical and radiological improvement was observed at one month after reduction of the steroid dose and addition of clarithromycin (79).

Data on cytotoxic and immunosuppressive agents for treating DIP are inconclusive. A limited number of studies reported favorable outcomes after azathioprine and methotrexate treatment (66). Lung transplantation may be the treatment of choice in cases with severe and persistent disease. However, recurrence may also be seen after transplantation (80-82).

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