Clinical Patterns of Diffuse Parenchymal Lung Disease in Kuwait: A Prospective Study

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Key Words

Pulmonary fibrosis · Pulmonary function test · Cigarette smoking · High resolution computed tomography · Lung biopsy

Abstract

Objective: To report our experience of the clinicopathological patterns of diffuse parenchymal lung disease (DPLD). **Subjects and Methods:** Over a 4-year period, 75 patients (41 males, 34 females), aged 13–76 years, who were referred to Mubarak Al-Kabeer and the Chest Diseases Hospitals, Kuwait with a diagnosis of diffuse lung disease, were included in the study. After a comprehensive history and physical examination, further investigations were done, including hematological and immunological profiles, sputum and bronchoalveolar lavage fluid examination, chest radiograph, high resolution computed tomography (HRCT), pulmonary function test and lung biopsy. **Results:** Of the 75 patients 60 (80%) were over 40 years of age. The duration of symptoms in 34 patients (45%) was less than 6 months and longer than 1 year in 28 (37.7%) patients. Twenty-five of the patients were cigarette smokers. The mean forced lung

capacity (FVC), total lung capacity and diffusing capacity for carbon monoxide were less than 60% of the predicted values in most patients. There was a significant difference in mean FVC value between smokers and nonsmokers ($p < 0.05$). The HRCT findings were at an advanced stage in 65 patients, with additional honeycombing in 21 of the 65 patients. Idiopathic pulmonary fibrosis was the most common cause of DPLD, occurring in 52 patients, followed by sarcoidosis and collagen vascular diseases. **Conclusion:** DPLD was observed predominantly in middle aged and elderly patients, due probably to increasing industrialization in the country. The role of cigarette smoking as a contributory factor remains unclear.

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Introduction

Many acute and chronic lung diseases of varying degrees of inflammation and fibrosis are collectively referred to as diffuse parenchymal lung disease (DPLD) or interstitial lung disease [1]. The etiology of many of these diseases remains unknown. However, since Hamman and Rich [2] described the clinical and morphologic features

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of 4 patients with progressive rapidly fatal diffuse pulmonary fibrosis, progress has been made in elucidating the clinicopathologic features of these diseases [1, 3–11].

A common pathologic feature, which is injury to the alveolar wall leading to the development of alveolitis with a subsequent loss of alveolar gas exchange, is found in many of these patients. Patients with these conditions present as a diagnostic and therapeutic challenge, the response to treatment being variable.

In the last three decades, Kuwait, an Arabian Gulf country, has witnessed an economic boom, leading to increased industrialization and an influx of migrant workers from neighboring countries, with attendant introduction of various health problems, among which has been the emergence of DPLD. However, since the only documented report on interstitial lung disease in Kuwait is limited to high resolution computed tomographic (HRCT) changes [12], documentation of the incidence, clinical characteristics and patterns of this cluster of lung diseases is of great importance. In this study, we report our experience on the clinicopathologic patterns of DPLD in Kuwait.

Subjects and Methods

This 4-year prospective collaborative, multidisciplinary study was carried out at two tertiary care hospitals (Mubarak Al-Kabeer and The Chest Diseases Hospitals) in Kuwait, between January 1997 and December 2000. Of the 75 patients, 41 were males and 34 females; mean age 51.1 ± 14.18 and median 52 years. Forty (53%) were Kuwaiti nationals, while the remaining 31 (47%) were non-Kuwaitis.

All the patients were referred from other hospitals and polyclinics either because of abnormal diffuse chest radiographic pattern or symptoms of progressive shortness of breath with abnormal radiographic features.

The inclusion of patients as DPLD was based on criteria adopted by Cushley et al. [8] and Raghu et al. [10]. After a comprehensive history and physical examination, all patients were subjected to investigations that included complete blood count, erythrocyte sedimentation rate, and full immunological profile, i.e. rheumatoid factor, antinuclear antibodies, anti-double-stranded DNA, complements, C-reactive protein, cytoplasmic and perinuclear antinuclear cytoplasmic antibodies, serum immunoglobulins, and precipitating antibodies to aspergillus and other specific antigens. A chest radiograph, followed by HRCT, was done routinely on all patients. The HRCT scans were interpreted by 2 radiologists, whose findings were based on consensus. Pulmonary function tests and arterial blood gases were carried out on the patients when feasible.

Bronchoscopy and transbronchial biopsy were performed on 33 patients. At least five pieces of lung tissue were sent for each biopsy to ensure that adequate tissue sample was available for processing and interpretation. Open lung biopsy was performed on 13 patients when considered necessary to reach a diagnosis if the transbronchial biopsy

report was inconclusive or not diagnostic. The open lung biopsy was carried out by the same thoracic surgeon in all cases while the lung histopathology was reported by 2 experienced pathologists.

Other relevant diagnostic investigations were done when indicated, including examination of sputum for acid-fast bacilli by direct smear and culture. Sputum was also examined cytologically (for malignant cells). Examination of bronchoalveolar lavage fluid for microorganisms, acid-fast bacilli and malignant cells was done.

Diagnosis

Using criteria adopted by Cushley et al. [8], a diagnosis of each DPLD was made as follows: (a) idiopathic pulmonary fibrosis (IPF): based on the presence of bilateral inspiratory crackles (with or without digital clubbing), HRCT, and histopathological findings [11]; (b) sarcoidosis: based on clinical features and lung tissue biopsy; (c) bronchiolitis obliterans organizing pneumonia (BOOP): based on criteria published by Epler et al. [13] and Colby [14], which include clinical features, evidence of pulmonary infiltrates on chest radiograph, HRCT findings, open lung biopsy and response to corticosteroids; (d) collagen vascular diseases: based on clinical features and relevant serological tests and tissue biopsy; (e) extrinsic allergic alveolitis/hypersensitivity pneumonitis: based on clinical features, relevant serological tests, tissue biopsy, and response to therapy; (f) Wegener's granulomatosis: based on clinical and radiographic features, combined with relevant serological test and tissue biopsy; (g) miliary tuberculosis: based on tissue biopsy, with characteristic histological features of caseating granuloma. The final diagnosis in each patient was reviewed by at least 2 pulmonologists.

Treatment

When the cause of DPLD was known, specific treatment was given. Patients with IPF who presented with symptoms/worsening of symptoms, coupled with significant restriction of pulmonary function tests and/or HRCT abnormalities, were given prednisolone alone in doses ranging from 30 to 40 mg/day for 8 weeks, with the dose tapering gradually to 10 mg/day. Azathioprine 100–200 mg was added to prednisolone in patients who did not improve either at 3 or 6 months.

In the case of sarcoidosis, treatment involved prednisolone in doses of 1 mg/kg body weight per day, which was subsequently tapered based on clinical response. Prednisolone therapy was also given to patients diagnosed with BOOP or extrinsic allergic alveolitis. Patients with Wegener's granulomatosis were treated with prednisolone and cyclophosphamide, and antituberculosis drugs were given to patients with miliary tuberculosis.

Follow-Up

All of the 75 patients were followed up every 3 months for 1 year. Their symptoms, pulmonary function tests, and when indicated, chest radiograph, were reviewed at each visit in the outpatient department.

Results

A summary of age distribution, symptoms, signs and radiographic investigations at presentation is given in table 1. Most of the patients (79.8%) were age 40 years

and over. The most common symptom was progressive shortness of breath, occurring in 93% of cases. Digital clubbing, associated with IPF, was observed in 75% of the cases. Ninety-three percent of the subjects had crackles, found mostly in the mid and late inspiratory phase of the respiratory circle (late inspiratory crackles were observed mainly in patients with IPF). Of the 75 patients, 34 (45%) had symptoms of less than 6 months in duration, while 28 (16%) had symptoms for over a year before presentation; 34% were cigarette smokers. IPF was the most common DLPD, occurring in 69% of the cases, followed by sarcoidosis, collagen vascular disease, BOOP and extrinsic allergic alveolitis (table 2).

Pulmonary Function Tests

Pulmonary function tests were restrictive in pattern in 87% of the subjects, while mixed restrictive and obstructive pattern was observed in the remaining 13% of the patients, mostly with rheumatoid lung disease and other connective tissue diseases. All the subjects diagnosed with IPF had restrictive lung pattern. The mean pulmonary function test parameters in patients with IPF are shown in table 3. A significant difference was also observed in the mean FVC value between smokers and nonsmokers ($p = 0.05$). The mean oxygen saturation at rest was $90.0 \pm 7.17\%$. Ten subjects had oxygen saturation below 90%, while 4 subjects had below 80% at presentation.

Table 1. Summary of age distribution, symptoms, signs and radiographic investigations at presentation

Variables	Cases	
	n	%
Age-groups		
<40	15	20
40–60	32	42.7
>60	28	37.1
Breathlessness	70	93.2
History of smoking		
Smokers	26	34
Never smokers	49	66
Digital clubbing	37	75
Crackles	70	93.2
Plain chest radiograph	75	100
HRCT scan	65	87

Table 2. Various patterns of DPLD

Disease	Cases	
	n	%
IPF	52	69.3
Sarcoidosis	6	8.0
BOOP	3	4.0
Rheumatoid arthritis	2	2.7
Scleroderma	2	2.7
Extrinsic allergic alveolitis	2	2.7
Wegener's granulomatosis	2	2.7
Miliary tuberculosis	2	2.7
Other connective tissue diseases	1	1.3
Lupus pneumonitis	1	1.3
<i>Pneumocystis carinii</i> pneumonia	1	1.3
Myeloproliferative disease	1	1.3
Total	75	100

Table 3. Mean pulmonary function test parameters in patients with IPF at presentation

Variables	Cases			Smokers			Nonsmokers			p value
	n	mean	SD	n	mean	SD	n	mean	SD	
FVC, % predicted	48	56.14	16.4	20	52.5	17.8	28	61.5	15.0	0.050
TLC, % predicted	48	67.0	16.8	20	61.8	16.7	28	66.6	13.1	0.241
RV, % predicted	48	92.05	37.3	20	93.6	42.6	28	94.5	32.0	0.933
TLCO, % predicted	48	57.60	20.7	20	51.97	12.0	28	57.6	22.1	0.280
% SO ₂	34	90.58	7.73	15	90.9	7.17	19	90.27	8.3	0.503

FVC = Forced vital capacity; TLC = total lung capacity; RV = residual volume; TLCO = diffusing capacity of carbon monoxide; SO₂ = oxygen saturation.

Radiological Tests

All the subjects had abnormal chest radiographs, mainly confluent reticular infiltrates or diffuse reticulonodular shadowing. Honeycomb features were reported in 18 (24%) of cases. The HRCT findings indicated that many of the subjects presented at an advanced stage (table 4). In most cases, HCRT revealed more than one abnormality that included peripheral/subpleural infiltrates, centrilobular infiltrates, intralobular interstitial thickening and traction bronchiectasis. In 21 (32%) of the cases, honeycomb appearance, in addition to other features, was recorded. HRCT findings suggestive of usual interstitial pneumonia, desquamative interstitial pneumonia (DIP) or nonspecific interstitial pneumonia were reported in patients with IPF.

An association was observed between these HRCT findings and similar histological subgroups in the tissue biopsy in some of the patients.

Response to Therapy

The response to therapy was not satisfactory in 50% of the subjects with IPF. The mean values for forced vital capacity, total lung capacity and diffusing capacity of carbon monoxide were stable at 3 months, but at 12 months, 48% of the subjects did not report for reevaluation and as such were lost to follow-up. Among the remaining 53% the pulmonary parameters had deteriorated in over 50% of them at the end of the monitoring period (table 5). Four (5%) died within in the 1-year period of follow-up.

However, 4 (5%) patients with the histological features of DIP showed some satisfactory response to prednisolone; their forced vital capacity value had increased after 3 months of observation although no further improvement was seen. Two of the patients with DIP also had radiographic improvement at the end of the observation period. Subjects treated for sarcoidosis, BOOP and extrinsic allergic alveolitis showed improvement clinically and radiographically at the end of the observation period. Those treated for collagen vascular disease had symptomatic relief, although no significant change in their pulmonary function and radiographic patterns was observed. The subjects treated for tuberculosis showed clinical and radiographic improvement at the end of the therapy.

Table 4. Findings from HRCT¹

HRCT findings	n	%
Ground glass appearance	35	53.8
Peripheral/subpleural infiltrates	40	61.5
Centrilobular reticular infiltrates	36	55.4
Intralobular interstitial thickening	40	61.5
Traction bronchiectasis	25	38.5
Honeycomb abnormality	21	32.3
Peripheral/subpleural emphysema	14	21.5

¹ Some cases had combined lesions.

Discussion

The number of cases documented over the period of our study may not be a true reflection of the extent of the disorders in Kuwait because some of the patients could have been treated in other institutions.

DPLD, which may remain undetected and only diagnosed once it has become irreversible, is likely more prev-

Table 5. Pulmonary function parameters at (1) presentation and (2) after 3 months of treatment of patients with IPF

Variables		n	Mean	SD	95% CI of the difference		
					lower	upper	p value
FVC	1	37	56.14	16.4	-2.9965	2.4765	0.848
	2		56.24	15.73			
TLC	1	37	67.0	16.8	-2.3463	2.2111	0.952
	2		64.18	15.3			
TLCO	1	37	57.64	20.7	-6.9718	3.7287	0.541
	2		57.24	17.54			

For abbreviations, see table 3.

alent than generally thought. The number of different forms, estimated at about 130 in the eighties, is now on the rise due to increasing exposure to new hazardous agents in industry, environmental pollution or administration of new drugs [15–17].

Although this study did not investigate the risk factors associated with DPLD, smoking was investigated because of its high prevalence in Kuwait [18].

Furthermore, smoking has been implicated as one of the environmental risk factors triggering DPLD, especially the idiopathic type [19–21]. Nagai et al. [20] suggested that chronic smoking is deeply involved in the pathogenesis of this disease and that it may influence the clinical course in terms of either disease severity or progression. However, since only one third of the patients in this study admitted to ever smoking, it appears that cigarette smoking was not a risk factor. Equally important is the fact that the proportion of males to females was 54.7% males and 45.3% females, similar to findings reported in other studies [22, 23]. The almost equal male-to-female ratio in all these studies is somewhat surprising since males habitually smoke more than females, thus de-emphasizing the impact of cigarette smoking on this disorder. Nevertheless, it remains possible that cigarette smoking may just be one of the risk factors involved in the pathogenesis of DPLD.

DPLD occurs predominantly in middle-aged and elderly patients [23, 24], consistent with our findings in which 80% of patients were over 40 years of age, with a mean of 52 years.

The most frequently encountered cause of DPLP was IPF (69%), followed by sarcoidosis, collagen vascular disease, and BOOP, respectively. The sequence of these DPLD-associated diseases is similar to that reported previously: IPF [12, 21, 24, 25–29], sarcoidosis [22], collagen vascular disease [21], and BOOP [21]. Rheumatoid ar-

thritis and scleroderma are the most frequently encountered collagen vascular diseases in Kuwait. Extrinsic allergic alveolitis was also encountered, although very few cases were found. Clinical history, indicating exposure to organic substances coupled with appropriate precipitating antibody test, and tissue lung biopsy and response to corticosteroid assist in confirming the diagnosis.

The predominance of IPF in this study cannot be satisfactorily explained. It has been well documented that HRCT has a high degree of accuracy in diagnosing many forms of DPLD [24, 26, 29]. Furthermore, it is unlikely that overdiagnosis could be a contributing factor as our diagnostic procedure involved extensive clinical investigation, HRCT findings, and confirmation by tissue biopsy (in many of the cases), in addition to the review of all cases by a minimum of 2 pulmonologists. Thus, the predominance of IPF in our study may be a true reflection of the high prevalence of this disorder in Kuwait.

Conclusion

DPLD was diagnosed mostly in subjects over 40, and among the cluster of DPLD diseases, IPF was by far the most common. The role of cigarette smoking as a contributory factor remains obscure.

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References

- 1 Crystal RG, Bitterman PB, Rennard SI, Hance AJ, Keogh BA: Interstitial lung disease of unknown cause: Disorders characterized by chronic inflammation of the lower respiratory tract. *N Engl J Med* 1984;310:154–166.
- 2 Hamman L, Rich AR: Acute diffuse interstitial fibrosis of the lungs. *Bull Johns Hopkins Hosp* 1944;74:177–212.
- 3 Felson B: A new look at pattern recognition of diffuse pulmonary disease. *AJR Am J Roentgenol* 1979;133:183–189.
- 4 Gaensler EA, Carrington CB: Open biopsy for chronic diffuse infiltrative lung disease: Clinical, roentgenographic, and physiological correlations in 502 patients. *Ann Thorac Surg* 1980;30:411–420.
- 5 Hunninghake GW, Fauci AS: Pulmonary involvement in the collagen vascular disease. *Am Rev Respir Dis* 1979;119:471–503.
- 6 Kelley MA, Daniele RP: Exercise testing in interstitial lung disease. *Clin Chest Med* 1984;5:145–156.
- 7 Mortenson RL, Bogin RM, King TE: Interstitial lung diseases; in Stretton TB (ed): *Recent Advances in Respiratory Medicine*, ed 4. Edinburgh, Churchill Livingstone, 1992, pp 163–182.
- 8 Cushley MJ, Davison AG, duBois RM, Egan J, Flower CD, Gibson GJ, Greening AP, Ibrahim NB, Johnston JD, Mitchell DM, et al: The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999;54:S1–S30.

- 9 American Thoracic Society/European Respiratory Society International Multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
- 10 Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD: The accuracy of clinical diagnosis of new onset idiopathic pulmonary fibrosis and other interstitial lung disease. *Chest* 1999;116:1168–1174.
- 11 Katzenstein AA, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;157:1305–1315.
- 12 Cherian JM, Dahniya MH, Abul A, Behbehani N, Khadadah M, Al-Marzouk N: High resolution computed tomography in diffuse interstitial lung disease. *Kuwait Med J* 1999;31:22–26.
- 13 Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA: Bronchiolitis obliterans organizing pneumonia. *N Engl J Med* 1985;312:152–158.
- 14 Colby TV: Pathologic aspects of bronchiolitis obliterans organizing pneumonia. *Chest Suppl* 1992;102:38S–43S.
- 15 Coulter DB: Epidemiology of idiopathic pulmonary fibrosis. *Semin Respir Med* 1993;14:181–196.
- 16 Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunninghake GW: Interstitial lung disease: Current concept of pathogenesis, staging and therapy. *Am J Med* 1981;70:542–568.
- 17 Memon A, Moody PM, Sugathan TN, El-Gerges N, Al-Bustan M, Al-Shatti A, Al-Jazzaf H: Epidemiology of smoking among Kuwaiti adults: Prevalence characteristics and attitudes. *Bull World Health Organ* 2000;78:1306–1315.
- 18 Hubbard R, Lewis S, Richards K, Johnston I, Britton J: Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. *Lancet* 1996;347:284–289.
- 19 Baumgartner KB, Samet J, Stidley CA, Colby TV, Waldron JA: Cigarette smoking: A risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1997;155:242–248.
- 20 Nagai S, Hoshino Y, Hayashi M, Ito I: Smoking related interstitial lung disease. *Curr Opin Pulm Med* 2000;6:415–419.
- 21 Grenier P, Valeyre D, Cluzel P, Brauner MW, Lenoir S, Chestang C: Chronic diffuse interstitial lung disease: Diagnostic value of chest radiography and high-resolution CT. *Radiology* 1991;179:123–132.
- 22 Roelandt M, Demedts M, Callebaut W, Coolen D, Slabbynck H, Bockaert J, Kips J, Brie J, Ulburghs M, DeBoeck K, Simons J, Van Meerbeeck K: Epidemiology of interstitial lung disease (ILD) in Flanders: Registration by pneumologists in 1992–1994. *Acta Clin Belg* 1995;50:260–268.
- 23 American Thoracic Society: Idiopathic pulmonary fibrosis: Diagnosis and treatment international consensus statement. *Am J Respir Crit Care Med* 2000;161:646–664.
- 24 Coultas DB, Zumwalt RE, Black WC, Sobonya RE: The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;150:967–972.
- 25 Muller NL: Computed tomography in chronic interstitial lung disease. *Radiol Clin North Am* 1991;29:1085–1093.
- 26 Mathieson JR, Mayo JR, Staples CA, Muller NL: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of CT and chest radiography. *Radiology* 1989;171:111–116.
- 27 Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part I. *Am Rev Respir Dis* 1990;142:1206–1215.
- 28 Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part II. *Am Rev Respir Dis* 1990;142:1440–1448.
- 29 Johnston ID, Prescott RJ, Chalmers JC, Rudd RM: British Thoracic Society study of cryptogenic fibrosing alveolitis: Current presentation and initial management. *Thorax* 1997;52:38–44.