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Lymphoid Interstitial Pneumonia: Clinical Features, Associations, and Prognosis

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Running Title: Features, Associations, and Prognosis of LIP

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Abstract:

Lymphoid interstitial pneumonia (LIP) is rare, and its clinical course incompletely described. The aim of this study was to examine the clinical features, associations, and prognosis of surgical lung biopsy-proven LIP.

The study group consisted of 15 subjects encountered over a 14-year period.

The majority of subjects were women (n=11), and the mean age was 47 years (17 to 78 years). Underlying systemic immune disorders were frequent, including Sjögren's syndrome (n=8), rheumatoid arthritis, systemic lupus erythematosus, polymyositis, common variable immunodeficiency, and dysproteinemia. Only three patients were classified as "idiopathic". Presenting symptoms were dominated by dyspnea and cough. Restrictive physiology, a reduced diffusing capacity (62.5 ± 18.4% predicted), and bronchoalveolar lavage lymphocytosis (30.5 ± 29.1%) were noted. Thirteen patients received corticosteroid therapy. Of the nine whose response could be assessed, four clinically improved and four were stable. Overall median survival was 11.5 years. Of the seven patients who died, the primary cause of death was respiratory in three. Conversion to lymphoma was not identified.

In conclusion, histopathologic LIP is commonly associated with immune system dysregulation, with idiopathic LIP being extremely rare. Clinical stability or improvement with corticosteroids can be expected, however survival remains impaired.

Key words: corticosteroid; lymphoid interstitial pneumonia; survival

INTRODUCTION

Lymphoid interstitial pneumonia (LIP) was originally described by Liebow and Carrington (1), as a benign lymphoproliferative disorder limited to the lungs and characterized by diffuse infiltration of the alveolar septa by dense collections of lymphocytes admixed with plasma cells and other cellular elements (Fig. 1A). Subsequent investigation has described it as a hyperplastic disorder of the mucosa-associated lymphoid tissues (MALT), lying on a spectrum of pathologic abnormalities that extends from follicular bronchiolitis to pseudolymphoma to LIP (3). In some classification schemes it has been considered a preneoplastic condition with a high likelihood of progression to lymphoma (4), however immunohistochemical and molecular analyses indicate that malignant transformation is unusual (5,6).

Histopathologic LIP is an uncommonly seen form of interstitial pneumonia, and its described clinical course is highly variable (8,9). Radiographic features are somewhat nonspecific, though cysts associated with ground glass infiltrates in a nonsmoker is a suggestive pattern (Fig. 1B). The pathologic finding has been associated with a variety of clinical conditions such as connective tissue disorders, especially Sjögren's syndrome, and other immune system abnormalities such as dysproteinemia, acquired immunodeficiency syndrome (AIDS), and bone marrow transplantation (10). Once underlying systemic diseases have been excluded, a diagnosis of "idiopathic" LIP can be made, and is classified with the idiopathic interstitial pneumonias (IIP) (7). As earlier reports of the clinical features of LIP included subjects with low-grade lymphoma (8,9,11,12), we have explored our prospectively collected clinical database to review our

experience with the clinical features and associations, response to treatment, and prognosis of this histopathologic entity.

METHODS

Subject Selection

We explored the prospectively collected clinical database of our Interstitial Lung Disease Program at the National Jewish Medical and Research Center for patients seen between January 1985 and December 1999. An informed consent was obtained from each patient, and the Institutional Human Subject Review Committee approved the protocol. Out of a total of 2989 subjects (1167 surgical lung biopsies) enrolled, 15 patients with histopathologically confirmed LIP were identified. The pathologic diagnosis was confirmed by review of the original biopsy material in all subjects by an expert pulmonary pathologist (CDC). Diagnosis was made by open lung biopsy (n=11); video-assisted thoracoscopic surgery (n=3); and transbronchial lung biopsy (n=1) with consistent high resolution computerized tomographic scanning (HRCT) (2). All subjects were HIV-negative. Subjects were classified as current smokers if they smoked cigarettes regularly within the previous year, former smokers if they had not smoked cigarettes in the previous year but had smoked in the past, and never smokers.

Clinical Assessment

A modified American Thoracic Society (ATS) questionnaire was used to collect demographic and clinical information (13). The degree of dyspnea was determined by a previously described dyspnea scale (13). Survival was assessed through April, 2003. Deaths were identified after the family contact or referring physician contact or by search of the national death registry. Patients were diagnosed with Sjogren's syndrome,

systemic lupus erythematosis, polymyositis and rheumatoid arthritis, if they met American College of Rheumatology criteria for the diagnosis.

Pulmonary Physiology and Bronchoalveolar Lavage (BAL)

Resting pulmonary function test (PFT) and cardiopulmonary exercise testing (CPET) were performed as previously described (13-19). Bronchoscopy with bronchoalveolar lavage (BAL) was performed after informed consent as previously described (20).

Assessment of Response to Treatment

Six months to one year after initial evaluation, response to treatment according to the international consensus for idiopathic pulmonary fibrosis (IPF) was assessed (21). Based on clinical, radiologic, and physiologic changes, the response was classified as improved, stable, or worse (21).

Statistical Analysis

Data were expressed as means ± standard deviation (SD). The Kaplan-Meier method was used to estimate survival. Survival time was calculated as the number of years from the patients' initial visit until death or time of censoring.

RESULTS

Clinical Characteristics

The clinical characteristics are summarized in Table 1. The male-to-female ratio was 1: 2.75. The age ranged from 17 to 78 years. Three quarters were never smokers (73.3%)

and one quarter former smokers. The duration of symptoms prior to evaluation ranged from two months to 12 years. Respiratory symptoms were more common than systemic complaints, and breathlessness was found in all patients. Chest examination often revealed bibasilar crackles, while digital clubbing was rare.

Associated Illnesses

Sjögren's syndrome was present in eight subjects (53.3%). Three patients had either rheumatoid arthritis, systemic lupus erythematosus, or polymyositis (Table 2). Two patients had a past history of hypothyroidism. One patient (case 14) was diagnosed with common variable immunodeficiency (CVID) one year prior to the diagnosis of the lung disease. In the seven patients who had serum protein electrophoresis and immunoelectrophoresis, dysproteinemia was detected in five patients: hypergammaglobulinemia in four and hypogammaglobulinemia in one. Consequently, three patients were classified as "idiopathic" LIP, although one of them (case 4) had monoclonal hypergammaglobulinemia.

Pulmonary Physiology (Table 3)

Values were consistent with a restrictive ventilatory disorder, including reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), elevated FEV_1/FVC, and reduced total lung capacity (TLC) and thoracic gas volume (Vtg). The uncorrected diffusing capacity for carbon monoxide (D_{LCO}) was decreased, and was associated with abnormal gas exchange during maximal exercise testing.

Analysis of Bronchoalveolar Lavage (BAL) Fluid

The total white blood cell count was increased and the predominant cell type was lymphocyte (Table 4). The number of T (CD3-positive) and B cells (CD21-positive) was within the normal range but T suppressor cells (CD8-positive) were increased as compared to T helper cells (CD4-positive).

Response to Treatment and Prognosis

Fourteen of 15 subjects were treated specifically for their lung disease. One patient (case 12) did not receive therapy because her lung involvement was symptomatically and physiologically mild and stable for several years. All fourteen were treated with corticosteroids and/or cytotoxic drugs including cyclophosphamide, azathioprine, and cyclosporin A (Table 5). Of these, two patients also received colchicine. Initial treatment was corticosteroids in 12 patients, and corticosteroids combined with methotrexate in one case. In case 2, a course of chloroquine preceded corticosteroid treatment. A response to therapy was evaluable on 10 subjects: eight (89%) showing either favorable (n=4) or stable (n=4) courses after steroid therapy. One patient (case 1) failed both corticosteroid and colchicine treatment and underwent single lung transplantation. Cyclophosphamide, azathioprine, and methotrexate were either combined with or replaced corticosteroids and the response was variable as shown in Table 5. Interestingly, the patient with CVID-related LIP (case 14) initially did not show improvement to corticosteroids and methotrexate, but did respond to cyclosporin A.

The median survival of the subjects was 11.5 years (Fig. 2). At the last follow-up, seven patients had died: two from end-stage lung disease; one, lung infection after lung transplantation; three, non-pulmonary causes; one, unidentifiable (Table 6). Thus, the progression of LIP to end-stage lung was found in three cases (cases 1, 2, 7). Malignant transformation to pulmonary lymphoma was not detected.

DISCUSSION

In the present study, we sought to define the clinical features, associations, and prognosis of biopsy-proven histopathologic LIP. As it is not routine at our center to perform surgical lung biopsy on all connective tissue disease patients with radiographic infiltrates, our cohort may not be inclusive of all LIP encounters at our center over the study period. In our patients the finding of LIP was characterized by female predominance, a frequent association with systemic immune disorders, restrictive physiology, BAL lymphocytosis, and impaired survival. Only three of fifteen cases were classified as idiopathic LIP. A response with stability or clinical improvement with corticosteroids was noted in most patients, while we documented one case of treatment-refractory LIP that appeared to respond to cyclosporin A.

Consistent with previous studies (11,22), the risk of transformation to malignant lymphoma appears to be low. While we did not identify any cases of transformation to pulmonary lymphoma, one patient with Sjögren's syndrome developed MALT lymphoma of the parotid gland and underwent successful surgical resection. A larger number of patients, followed for longer periods of time, is needed to answer this question

definitively. Two cases were associated with breast cancer which was diagnosed before or after diagnosis of LIP, respectively. However, the relationship between LIP and breast cancer is unclear.

Most patients (8/9) treated with corticosteroids were clinically stable or improved. To date, corticosteroids have usually been the primary therapeutic regimen in LIP (23), although there have been no controlled clinical trials because of its low incidence. It is unclear whether treatment alters the natural course of LIP (21). Other immunosuppressive agents, such as cyclophosphamide, azathioprine, and chlorambucil, have been used anecdotally (12,24). In this study, cyclophosphamide, azathioprine, and colchicine were used, but the response was variable. A recent report (25) suggested a role for cyclosporin A in CVID-related LIP. Cyclosporin A has a complex action, but the principal immunosuppressive effect is inhibition of CD4-positive Th2 lymphocyte activation and the related release of IL-4 and IL–5, thus inhibiting clonal expansion of T cells without directly affecting B cells (25,26). In our cohort, case 14 with CVID-related LIP improved clinically with cyclosporin A after no improvement with steroids.

From our study the IIP idiopathic LIP, appears to be very rare, with only 3 patients seen in a busy tertiary referral ILD program over a 15 year period. It should also be recognized that our identification of these three cases represents a maximal estimate. As we did not prospectively define the evaluation for autoimmunity or immune dysregulation in these patients, we cannot fully exclude the possibility that we missed an otherwise occult systemic disorder. Of the three idiopathic cases, two (cases 4, 5) were

alive at the final check, surviving more than 10 years, with the response to steroids favorable in case 4 and failure in case 5. The third (case 2) had survived over 20 years despite progression to end-stage lung. As case 2 underwent open lung biopsy and received chloroquine and steroids about 13 years before referral to our program, the response to treatment was not evaluable. While 1 of 3 idiopathic LIP cases had died at last followup, as opposed to 6 of 12 non-idiopathic cases (Fig. 2), the low numbers and retrospective nature of our study preclude any firm statements on comparative prognosis. Similarly, it is intriguing that 3 of 3 cases of idiopathic LIP were male, whereas 11 of 12 non-idiopathic cases were female.

Despite the high prevalence of systemic immune disorders in our cohort, 3 of the 6 deaths for which causes were identifiable were respiratory in nature. This finding suggests that LIP may have an independent impact on survival. Of interest in this regard, it has been reported that granulomatous-lymphocytic interstitial lung disease (GLILD), a classification that includes LIP, is associated with worsened survival among patients with an underlying diagnosis of CVID (27). In that report, CVID patients with GLILD were found to have a median survival of 13.7 years (27), very similar to the median survival of 11.5 years noted for LIP in our study.

We also sought to address some of the "areas of uncertainty" in LIP research proposed in the Joint Statement of ATS/ ERS (7), including incidence and prevalence of LIP, frequency of idiopathic LIP, its malignant potential, and whether corticosteroids alter the natural history. Our data suggest that, given the rarity of this disease, a large, multi-

centered, multi-national effort will be necessary to answer the majority of these proposed questions.

In conclusion, histopathologic LIP is an uncommon ILD with idiopathic LIP being extremely rare. Similar to other ILDs, physiologic restriction and abnormal gas exchange are common, and the expected BAL lymphocytosis is present. Clinical stability or improvement in response to corticosteroids may be expected, however survival is impaired. Large multi-centered trials will be necessary to further our understanding of this disorder.

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Figure 1. Pathologic and Computed Tomographic Findings of Lymphoid Interstitial Pneumonia. *A,* Histopathologic features include diffuse lymphocytic infiltrates with granuloma formation. *B,* Computed tomographic findings are nonspecific but include mixed alveolar-interstitial infiltrates and thin-walled cysts.

Figure 2. Survival curve of patients with lymphoid interstitial pneumonia. The median survival was 11.5 years.

Table 5. Response to therapy in those subjects in whom follow-up was available. Response is defined by the ATS consensus criteria for monitoring of idiopathic pulmonary fibrosis (21). Clinical response was defined as a clinically significant change in dyspnea and/or cough; radiographic response as a measureable change in radiologic opacities, and physiologic response as >= 10% change in FVC and/or TLC or >=15% change in DLCO. Response in all subjects was measured at 6-12 months after diagnosis. Definition of abbreviations: MTX, methotrexate; ↑, improvement; →, no change; ↓, decrease; NA, not available. * Idiopathic lymphoid interstitial pneumonia. In the treatment column, consecutive therapies are listed in chronological order.

Table 1. Clinical Characteristics (n=15)

Gender (M/F)		4/11
Age (years)		47.1 ± 18.9
Race	Caucasians	13 (86.7%)
Smoking status	Never-smoker	11 (73.3%)
	Former smoker	4 (26.7%)
Symptoms		
Constitutional	Fatigue	13 (86.7%)
	Fever	5 (33.3%)
	Unintentional weight loss	5 (33.3%)
	Arthralgia	6 (40.0%)
Respiratory	Duration of respiratory symptoms (years)	2.8 ± 3.2
	Cough	8 (53.3%)
	Sputum	5 (33.3%)
	Dyspnea	11/11 (100%)
	Grades of dyspnea*	Grade 3-10
	Durations of dyspnea (years)	2.7 ± 3.2
Physical findings		
	Basilar crackles	11 (73.3%)
	Wheezing	1/13 (7.7%)
	Clubbing	2 (13.3%)

Table 2. Underlying Conditions

Patient No.	Sex	Age	Dysproteinemia	Sjögren's syndrome	Other connective tissue diseases	Hypothyroidism	Malignancy
1	F	50			RA		
2*	M	17					
3	F	28	Hypergammaglobulinemia	+	SLE	+	Parotid gland MALToma
4*	M	62	Hypergammaglobulinemia Monoclonal gammopathy				
5*	M	52					
6	F	43				+	
7	F	28		+			
8	F	54	Hypergammaglobulinemia	+			Breast cancer
9	F	60					
10	F	78	Hypergammaglobulinemia	+			Breast cancer
11	F	41		+	Polymyositis		
12	F	75		+			
13	M	18	Hypogammaglobulinemia	+			
14	F	37	CVID				
15	F	61		+			

Definition of abbreviations: RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MALT = mucosa-associated
lymphoid tissue; CVID = common variable immunodeficiency.
* Idiopathic lymphoid interstitial pneumonia

Table 3. Lung Function Testing

Parameters	LIP	n
FEV_1 (% pred)	67.3 ± 18.4	15
FVC (% pred)	65.0 ± 15.0	15
FEV_1/FVC (%)	80.3 ± 5.0	15
TLC (% pred)	78.2 ± 16.1	13
Vtg (% pred)	77.5 ± 16.8	13
RV (% pred)	120.5 ± 36.3	13
R_{AW} (% pred)	135.1 ± 56.8	13
D_{LCO} (% pred)	62.5 ± 18.4	13
D_{LCO}/V_A (% pred)	93.6 ± 22.2	13
Resting $P(A\text{-}a)O_2$ (mmHg)	17.2 ± 8.6	12
Peak $P(A\text{-}a)O_2$ (mmHg)	42.9 ± 10.5	10

Definition of abbreviations: LIP=lymphoid interstitial pneumonia.
Values are mean ± SD.

Table 4. Analysis of Bronchoalveolar Lavage Fluid

Parameter	Values	n
WBC count ($x10^6$)	60.6 ± 40.5	6
Differential count (%)		
Alveolar macrophage	44.5 ± 28.6	6
Neutrophils	17.5 ± 17.3	6
Eosinophils	7.5 ± 7.0	6
Lymphocytes	30.5 ± 29.1	6
T cells (CD3)	75.7 ± 27.7	3
T-helper cells (CD4)	30.3 ± 33.5	3
T-suppressor cells (CD8)	37.3 ± 33.7	3
B cells (CD21)	0.8 ± 1.1	6

Values are mean ± SD.

Table 5. Response to Treatment

Patient No.	Treatment	Clinical Response	Radiologic Response	Physiologic Response	
				TLC/ or FVC	D_{LCO}
1	Steroid Colchicine	↑	→	→	→
3	Steroid	↑	↑	↑	↑
4*	Steroid	↑	↑	↑	↑
5*	Steroid	→	↓	→	↓
6	Steroid	NA	↑	↑	↑
7	Steroid Cyclophosphamide Colchicine	→ ↓ ↑	↓ ↓ →	→ → →	→ → →
8	Steroid	↑	→	↓	→
13	Steroid Cyclophosphamide Azathioprine	→	→	↓	→
14	Steroid Cyclosporin A	→ ↑	↑ ↑	→ ↑	→ →
15	Steroid + MTX Cyclophosphamide	↑ ↑	↑ ↑	↓ →	→ →

Table 6. Prognosis and Cause of Death

Patient No.	Prognosis	Cause of death
1	Dead	Following lung transplant
2*	Dead	End stage lung
3	Alive	-
4*	Alive	-
5*	Alive	-
6	Alive	-
7	Dead	End stage lung
8	Dead	Non-pulmonary cause
9	Alive	-
10	Dead	Congestive heart failure
11	Dead	NA
12	Dead	Non-pulmonary cause
13	Alive	-
14	Alive	-
15	Alive	-

Definition of abbreviations: NA = not available.
* Idiopathic lymphoid interstitial pneumonia.

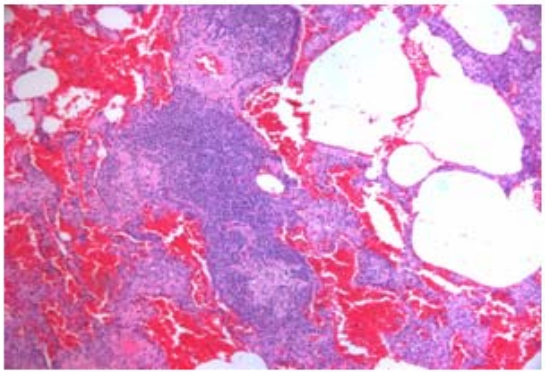


Figure 1A

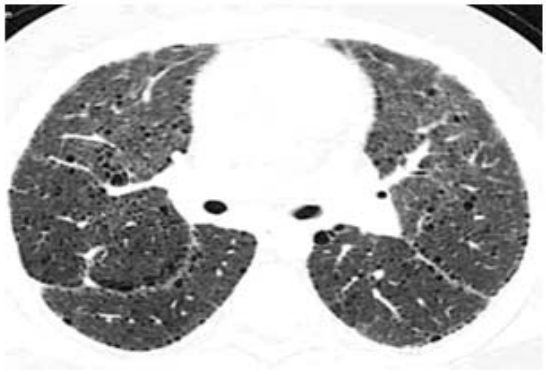
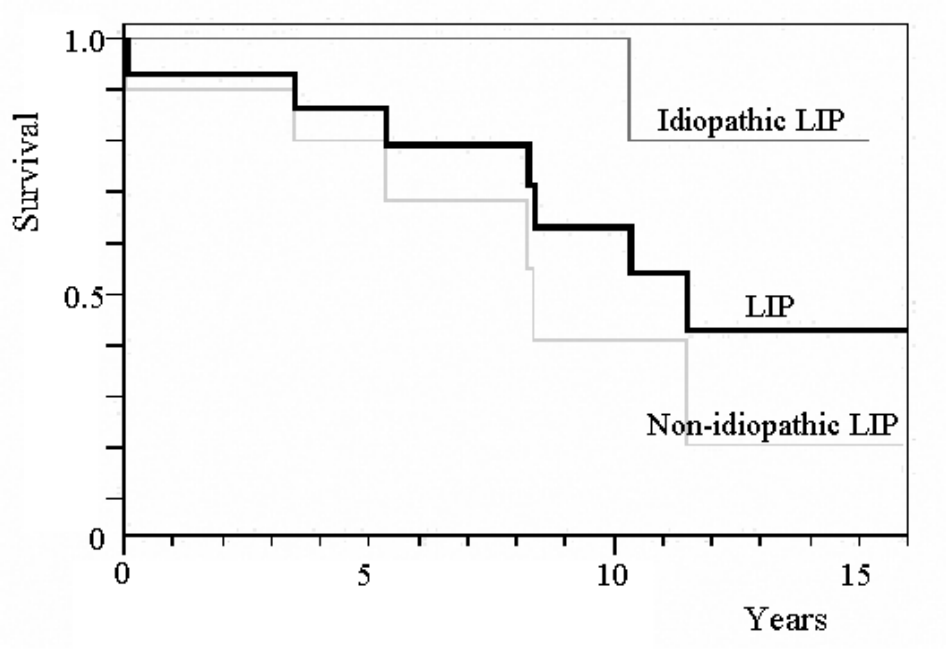


Figure 1B


1.0
0.5
0
Survival
0
5
10
15
Years
Idiopathic LIP
LIP
Non-idiopathic LIP