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Lymphocytic Interstitial Pneumonia in a Patient with Primary Sjögren Syndrome: A Case Report

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ABSTRACT

Lymphocytic interstitial pneumonia is a rare lymphoproliferative disease involving the lung. It commonly occurs in rheumatological conditions. Among them, primary Sjögren syndrome is the most common association. We report a rare case of lymphocytic interstitial pneumonia in a patient with primary Sjögren syndrome. A 65 years old previously healthy female initially presented to the respiratory clinic with a history of progressive exertional dyspnea without other respiratory symptoms, anemic symptoms or features of heart failure, diagnosed as a lymphocytic interstitial pneumonia and then one year later she develop dry eyes and dry mouth without evidence of other autoimmune disorder and found to have primary Sjögren syndrome. Initially she was treated with prednisolone for lymphocytic interstitial pneumonia then treated with hydroxychloroquine, artificial tears and chewing gum for Sjögren syndrome. Her respiratory symptoms and lung functions were improved with prednisolone. Her symptoms of dryness also improved. Although rare, lymphocytic interstitial pneumonia is a well-known association with primary Sjögren syndrome. It can be developed before the diagnosis of Sjögren syndrome as in this patient; therefore, screening for Sjögren syndrome and other rheumatological disorders is warranted in a patient with lymphocytic interstitial pneumonia. Steroid is the mainstay of treatment of lymphocytic interstitial pneumonia.

Lymphocytic Interstitial Pneumonia (LIP) is a rare pulmonary lymphoproliferative disorder named due to the diffused infiltration of lymphocyte and plasma cells in histological specimens [1]. LIP is commonly associated with autoimmune disorders. Among them, Sjögren syndrome is the most common. Other associations are infection due to human immunodeficiency virus and Ebstein-Barr virus [2]. Sjögren syndrome is an autoimmune disease that mainly affects the

exocrine glands in the eyes and mouth and presents with dryness of the eyes and mouth. It is classified as primary in the absence of systemic autoimmune disease or otherwise secondary. Even though primary SS primarily affects the exocrine glands of the eyes and mouth, it can cause systemic manifestations as well. Among them, pulmonary manifestations are well recognized [3]. Here, we present a case of LIP associated with primary Sjögren syndrome.

Case presentation

A 65-year-old previously healthy female presented to the respiratory clinic with a history of progressive exertional dyspnea for 3 months duration. She developed dyspnea after walking at nearly 100m. Her dyspnea was not associated with fever or cough. There was no orthopnea, paroxysmal nocturnal dyspnea or ankle swelling. There were no anemic symptoms other than this exertional dyspnea. There were no constitutional symptoms as well. There were no features of connective tissue disorder or symptoms of dryness of mouth or eyes.

On general examination, she was averagely body build, not pale, not icteric, with normal jugular venous pressure, no finger clubbing, and no ankle edema. Her respiratory system examination was only remarkable for fine bi-basal crepitation. Her cardiovascular system examination was unremarkable as was the abdominal examination.

Her initial investigation revealed a normal full blood count, increased Erythrocyte Sedimentation Rate (ESR) with normal C-reactive protein, and chest x-ray revealed mild bilateral reticular opacities. Further investigations revealed a negative Mantoux test, negative rheumatoid factor, and positive anti-nuclear antibody (Table 1). Her electrocardiogram (ECG) and 2D echocardiogram were normal. Her initial lung function test revealed a mild reduction in vital capacity without any restriction or obstruction (Figure 1), and the lung diffusion test revealed a severe reduction in diffusing capacity (Figure 2). Her high-resolution computed tomography (HRCT) chest demonstrated thin wall cysts scattered in all zones bilaterally with minimal ground glass infiltrates in mid and upper zones bilaterally are suggestive of lymphocytic interstitial pneumonia (Figure 3).

She started on prednisolone at the dose of 0.5mg/kg (35mg) and tailed off gradually. She was treated with prednisolone for four months duration. Her symptoms were gradually improved. After completion of treatment, she underwent a repeat HRCT chest, which showed no interval changes, and a lung functions test, which showed improvement in Residual Volume (RV), Total Lung Capacity (TLC), Diffusing Capacity (DLCO), and decline in Forced Vital Capacity (FVC) (Figure 4).

Almost one year after the onset of initial symptoms, she developed dryness in her eyes and mouth. There were no features suggestive of dehydration, and she was not on diuretics. There were no associated constitutional symptoms. Except for mild small joint pain in bilateral hands, no features of other connective tissue disorders. On examination, mild dryness of the eyes and mouth was noted. There was no evidence of synovitis in bilateral hands. Other general and systemic examinations were unremarkable other than mild bilateral fine crepitations in the lungs. Schirmer's test demonstrated bilateral severe eye disease. Her basic investigations were unremarkable other than moderate elevations in ESR.

Other than the usage of tear substitute, she had four out of five features of inclusion criteria and none of the exclusion criteria of ACR/EULAR classification criteria for primary Sjögren syndrome. Her Extractable Nuclear Antigen (ENA) panel was negative including anti-Ro and

anti-La (Table 2). She refused for a lip biopsy. In the absence of an alternative diagnosis, primary Sjögren syndrome was diagnosed. She was treated with artificial tears twice daily for dry eyes and dry mouth; she was advised to take sips of water frequently, use lip balm and salivary patches as needed, and hydroxychloroquine 200mg at night for small joint pain. Her symptoms of dryness and small joint pain were improved.

Table 1

Investigations

Investigations	Reference range	Patient's value
WBC	4000 – 10,000/μL	8,140/μL
Neutrophil	50% - 70%	49.8%
Lymphocyte	20% - 40%	39%
Hemoglobin	13.2 – 16.5g/dl	14g/dl
MCV	80.0 – 100.0fL	93.3fL
Platelet	150,000 – 400,000/μL	278,000/μL
ESR	<20mm/1st hour	68/1st hour
CRP	0 – 5mg/L	5mg/L
Creatinine	70 – 115μmol/L	58.3μmol/L
Urea	8 – 50mg/dl	20.8mg/dl
Sodium	137 – 147mmol/L	139mmol/L
Potassium	3.5 – 5.1mmol/L	5mmol/L
Calcium	2.15 – 2.57mmol/L	2.3mmol/L
AST	0 – 35U/L	16U/L
ALT	0 – 40U/L	32U/L
UFR	-	No albumin or RBC
Retrovirus antibody	Negative	Negative
Hepatitis C IgM	Negative	Negative
Rheumatoid factor	0 – 20 IU/mL	5.2
ANA	< 1:80	Nuclear and cytoplasmic pattern positive 1:80

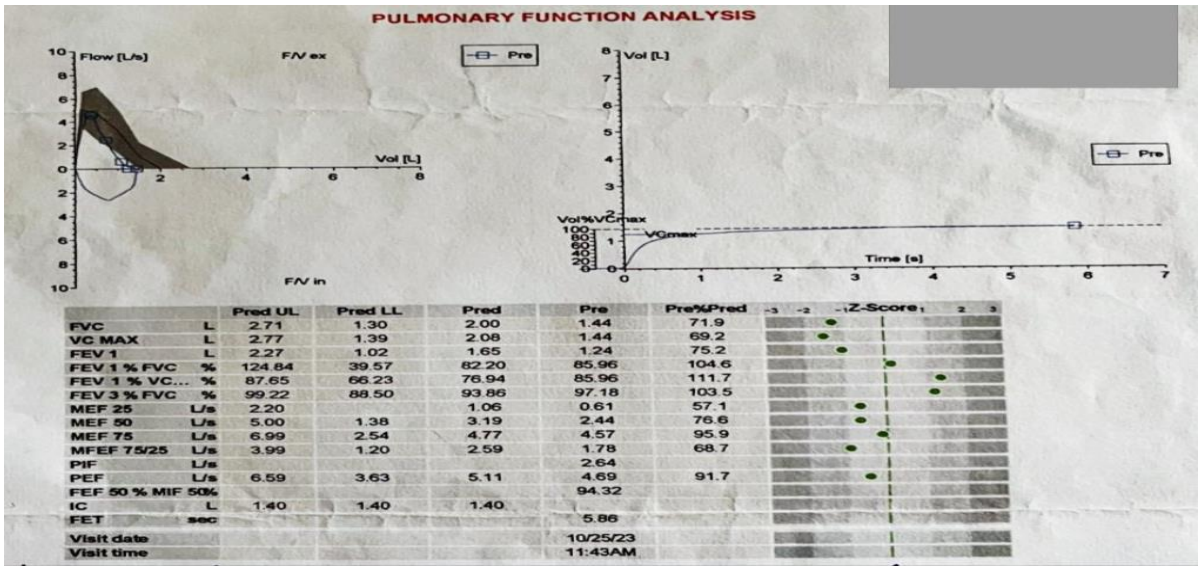
WBC – white blood cells, MCV – mean corpuscular volume, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, UFR – urine full report, RBC – red blood cells, ANA – anti nuclear antibody.

Table 2

ENA Panel

ENA profile	Result
RNP/Sm antibody	Negative
Sm antibody	Negative
SS-A/ Ro antibody	Negative
Ro-52 antibody	Negative
SS-B/ La antibody	Negative
Scl 70 antibody	Negative
PM-Scl antibody	Negative
Anti-Jo 1 antibody	Negative
Anti-centromere (B) antibody	Negative
PCNA antibody	Negative
Anti-DS DNA antibody	Negative
Nucleosome antibody	Negative
Anti-histone antibody	Negative
Ribosomal P antibody	Negative
Anti-mitochondial (M2) antibody	Negative

Figure 1. Pulmonary function test showing mild reduction in vital capacity without obstruction or restriction.



		Pred UL	Pred LL	Pred	Pre	Pre%Pred
FVC	L	2.71	1.30	2.00	1.44	71.9
VC MAX	L	2.77	1.39	2.08	1.44	69.2
FEV 1	L	2.27	1.02	1.65	1.24	75.2
FEV 1 % FVC	%	124.84	39.57	82.20	85.96	104.6
FEV 1 % VC...	%	87.65	66.23	76.94	85.96	111.7
FEV 3 % FVC	%	99.22	88.50	93.86	97.18	103.5
MEF 25	L/s	2.20		1.06	0.61	57.1
MEF 50	L/s	5.00	1.38	3.19	2.44	76.6
MEF 75	L/s	6.99	2.54	4.77	4.57	95.9
MFEF 75/25	L/s	3.99	1.20	2.59	1.78	68.7
PIF	L/s				2.64	
PEF	L/s	6.59	3.63	5.11	4.69	91.7
FEF 50 % MIF 50%					94.32	
IC	L	1.40	1.40	1.40		
FET	sec				5.86	
Visit date					10/25/23	
Visit time					11:43AM	

Figure 2. Lung diffusion test showing severe reduction in diffusing capacity with low KCO.

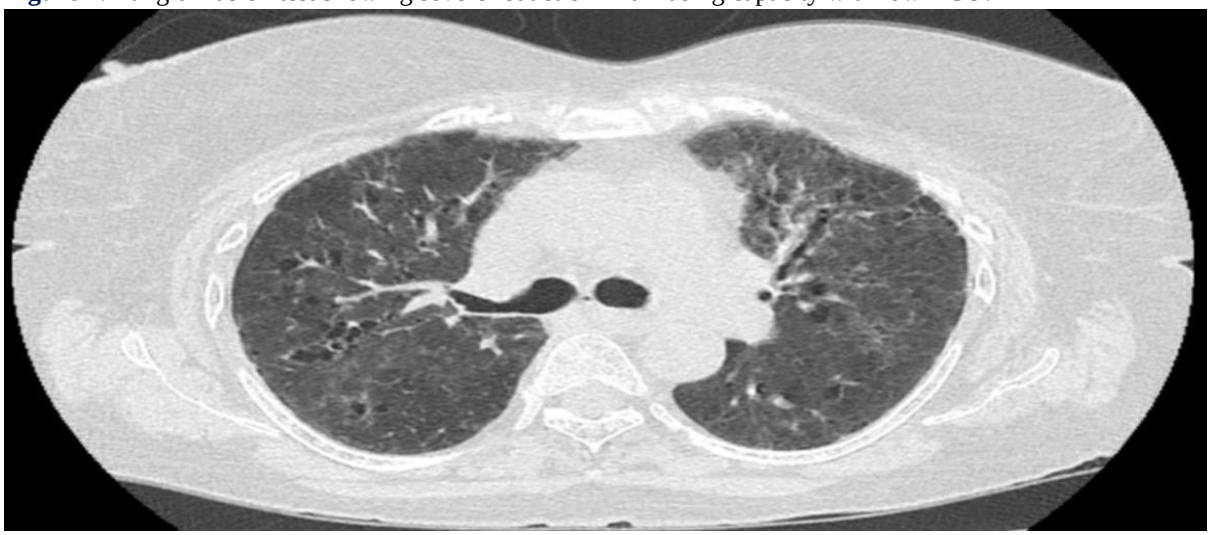
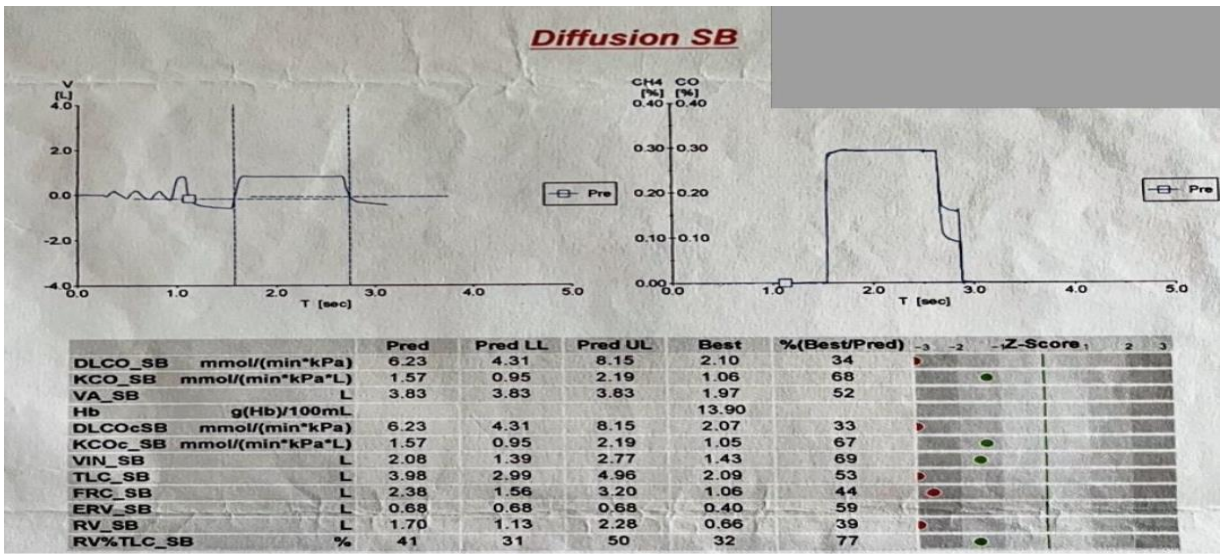
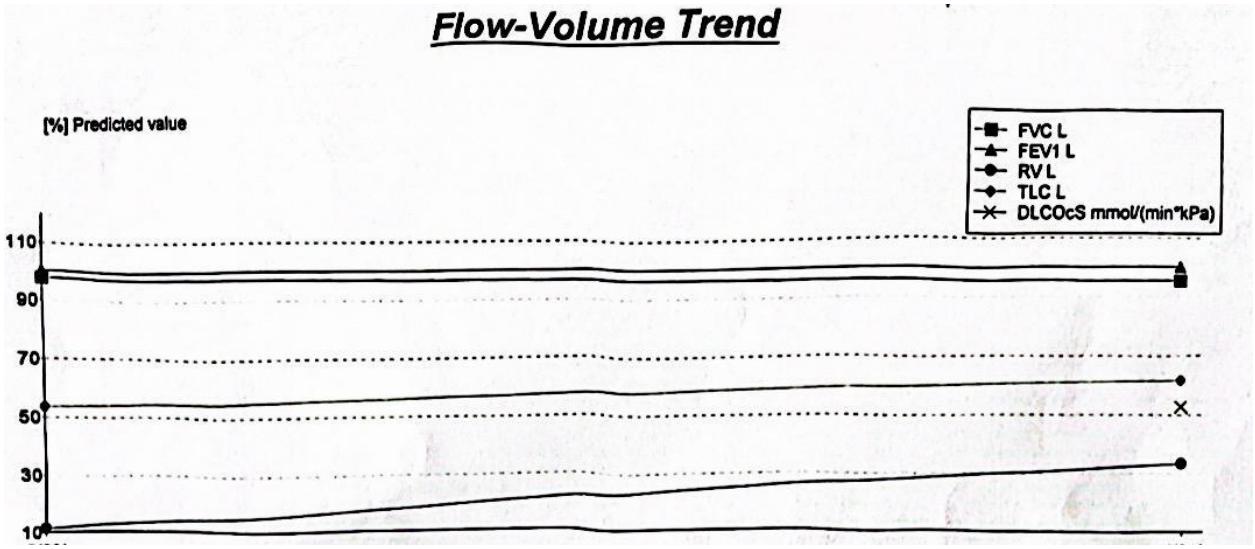


Figure 3. HRCT chest showing thin wall cysts scattered in all zones bilaterally with minimal ground glass infiltrates.



		Pred	Pred LL	Pred UL	Best	%(Best/Pred)
DLCO_SB	mmol/(min*kPa)	6.23	4.31	8.15	2.10	34
KCO_SB	mmol/(min*kPa*L)	1.57	0.95	2.19	1.06	68
VA_SB	L	3.83	3.83	3.83	1.97	52
Hb	g(Hb)/100mL				13.90	
DLCOcSB	mmol/(min*kPa)	6.23	4.31	8.15	2.07	33
KCOc_SB	mmol/(min*kPa*L)	1.57	0.95	2.19	1.05	67
VIN_SB	L	2.08	1.39	2.77	1.43	69
TLC_SB	L	3.98	2.99	4.96	2.09	53
FRC_SB	L	2.38	1.56	3.20	1.06	44
ERV_SB	L	0.68	0.68	0.68	0.40	59
RV_SB	L	1.70	1.13	2.28	0.66	39
RV%TLC_SB	%	41	31	50	32	77

Figure 4. Comparison of lung functions test before and after treatment with prednisolone.



Before initiation of treatment

After completion of treatment

Discussion

LIP is histopathologically best described as diffuse pulmonary lymphoid hyperplasia with interstitial changes. LIP has a female predominancy and is commonly present in the fifth decade. It typically presents as a gradual progressive worsening of dyspnea and cough. Systemic symptoms such as fever and weight loss are occasionally encountered. Even though LIP is categorized as a pulmonary lymphoproliferative disorder, only a small number of cases transform into malignancy [4].

The main radiographic features are perivascular cysts, ground glass opacity, and reticular abnormalities [4]. As the radiographic features are non-specific lung biopsy or bronchoalveolar lavage is required for the diagnosis of LIP [5]. The bronchoalveolar lavage may demonstrate lymphocytes. The key histological finding is diffuse interstitial infiltration by lymphocytes, plasma cells, and histiocytes [4]. In contrast to monoclonal B cell infiltration in malignant lymphoma, lymphocytes in LIP are polyclonal T and B cells [6]. In this case, LIP is diagnosed by the presence of lymphocytes in bronchoalveolar lavage, bilateral cystic lesions, and ground glass appearance in the HRCT chest.

There are no randomized trials for the management of LIP, and the current practice is largely based on case reports. Prednisolone is the mainstay of therapy. The clinical course is widely variable. Some patients improved without any treatment, and some patients progressed to fibrosis despite immunosuppressive therapy. According to available data, most of the patients (50 to 60%0 responded to prednisolone including complete remission in few cases. The initial dose of the prednisolone is 0.75 to 1mg/kg/d for 8 to 12 weeks and then gradual tapering over 6 to 12 weeks. Cyclophosphamide and chlorambucil also have been used [2].

Sjögren syndrome is a chronic multisystemic autoimmune disorder that primarily affects lacrimal and salivary glands and presents as dry eyes and mouth as a key clinical feature. Histologically, it is characterized by lymphocytic infiltration of the affected exocrine gland [3].

Sjögren syndrome can be a part of the multisystem involvement of systemic autoimmune disorders, where it is defined as secondary and, in the absence of other autoimmune disorders, defined as primary [7]. Sjögren syndrome also affects extra glandular organs including the skin, heart, lung, gastrointestinal tract, and liver [3]. Nonspecific interstitial pneumonia (NSIP) is the most common pulmonary manifestation of systemic autoimmune rheumatic disorder. Even though LIP is not common but has a strong association with primary Sjögren syndrome [4].

Primary Sjögren syndrome is diagnosed by the ACR/EULAR classification criteria for primary Sjögren syndrome. These criteria apply to a suspected patient with Sjögren syndrome who meets any of the five inclusion criteria and has no exclusion criteria [8]. A score of four or more is classified as primary Sjögren syndrome. In this case, the patient had only one score and refused the lip biopsy, and primary Sjögren syndrome was diagnosed in the absence of an alternative diagnosis.

Treatment of Sjögren consists of two aspects, treatment of ocular and oral dryness and treatment of active systemic disease. Treatment of interstitial lung disease in Sjögren syndrome is common for any type of interstitial lung disease. Systemic steroid is the first line treatment in the dose of prednisolone 0.5 to 1mg/kg/day. Azathioprine and mycophenolate should be considered when there is a poor response to initial therapy or long-term steroid are needed. If there is a poor response to Azathioprine or mycophenolate or intolerance to either drug rituximab or calcineurin inhibitors may be used. Patients with mild symptoms usually require a disease modifying agents either hydroxychloroquine or methotrexate [9].

Conclusion

Lymphocytic interstitial pneumonia is a rare lymphoproliferative disease involving the lung. Although not common but has a well-known association with primary Sjögren syndrome. It can be developed before the diagnosis of Sjögren syndrome as in this patient; therefore, screening for Sjögren syndrome and other rheumatological disorders is warranted in a patient with lymphocytic interstitial pneumonia. As radiological features are non-specific, bronchoalveolar lavage or lung biopsy is required for the diagnosis. Steroid is the mainstay of treatment of lymphocytic interstitial pneumonia based on case reports with favorable outcome with most of the patients including this patient.

Declarations

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Ethics Approval

Not applicable.

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