Case Report

# Case-based discussion: Lymphocytic interstitial pneumonia a rare presentation in an immunocompetent adult male

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## ABSTRACT

Lymphocytic interstitial pneumonia (LIP) is a rare form of interstitial lung disease usually associated with other systemic diseases; however, idiopathic cases are being reported. As per recent ATS/ERS 2013 guidelines, diagnostic criteria of clinical, radiological and histopathological for LIP is same as 2002 except some cystic changes on HRCT chest. Many cases diagnosed in the past as LIP now turn out to be NSIP; therefore as per new ATS/ERS classification whenever anybody report a case of LIP, NSIP should always be kept in mind as differential diagnosis. Here we present a case of LIP in an immunocompetent adult male presented with history of persistent dry cough and breathlessness on exertion, confirmed on HRCT chest and histopathologically, treated successfully with steroids.

**KEY WORDS:** Common variable immunodeficiency syndrome, human immunodeficiency virus, interstitial lung disease, nonspecific interstitial pneumonitis, sjogrens syndrome, steroids

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## INTRODUCTION

Lymphocytic interstitial pneumonia (LIP) is one of the rarest of the interstitial lung disease characterized by the infiltration of the lymphoid cells in the expansion of interstitium which are benign histologically and polyclonal immunophenotypically. Lymphocytic interstitial pneumonia may be idiopathic or associated with other systemic or autoimmune diseases.[1] It has also been reported in association with human immunodeficiency virus infection and common variable immunodeficiency syndrome. Although it is a benign disease, transformation to lymphomas occurs in few (5%) cases, 5-year survival has been reported in about in 50-60% cases. The main symptoms are gradual onset of persistent progressive dry cough and breathlessness, which is often associated with constitutional symptoms. Diagnosis is confirmed on chest radiograph, HRCT chest along with histological examination. The natural history and clinical course of LIP is quite variable[1-5] with few patients recover without treatment, some improve with corticosteroids, about 1/3rd may progress to end-stage fibrosis and respiratory failure. LIP is steroid-responsive disease, but sometimes immunosuppressive therapy is required for recovery along with oxygen supplementation on blood gas analysis and exercise-induced hypoxemia.

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## CASE REPORT

A 24-year-old gentleman presented with 3-months history of persistent dry cough, and breathlessness on exertion, no history of fever, hemoptysis, chest pain, loss of appetite, weight loss, allergy, asthma, or any major illness in the past. A student, non-smoker, family history of atopy present. Despite antibiotics and symptomatic treatment continue to deteriorate. His general physical examination was normal, with pulse rate of 88/minute, blood pressure 110/68 mmHg, respiratory rate 22/minute, J.V.P. not raised, cyanosis, lymphadenopathy, clubbing, were not present. Chest examination revealed bibasilar crackles. There were no signs of Sjogrens syndrome or other autoimmune disease. Arterial blood gas measurements revealed respiratory alkalosis with mild hypoxemia. A suspicion of Sarcoidosis, hypersensitivity pneumonitis, was made. His routine hemogram was normal except mild leucocytosis and no eosinophilia. Biochemical indices, urine analysis, and SACE were normal. Antinuclear antibody, C-ANCA,

P-NCA, and rheumatoid factor were negative. HIV panel, HCV, HBsAg, EBV serological test were non-reactive. As patient was already started on steroids before coming to us therefore immunoglobulin levels were not done. Sputum examination for Grams staining and A.F.B. were negative. Sputum culture examination for bacterial, fungal and mycobacteria were sterile. Sputum examination for *Pneumocystis jiroveci* could not be done. Chest radiograph showed bilateral extensive haziness and reticulation [Figure 1]. Computed tomographic scan of chest [Figure 2] revealed ill-defined patchy ground glass densities predominantly in bilateral lower lobes more in the periphery with peribronchovascular interstitial thickening and fissural irregularity, mediastinal lymph nodes enlargement not seen. Pulmonary function test revealed mild restrictive defect with decreased carbon monoxide diffusion capacity. Patient underwent thoracoscopic lung biopsy. Histology showed [Figure 3] irregular thickening of alveolar septa due to nodular lymphocytic infiltrate, in some of the infiltrates a few foamy histiocytes and rarely a giant cell were seen, few isolated calcified foreign body giant cells were noted, a few small groups of alveoli were filled with pale staining histiocytes, in few fields small foci of fibrosis were seen in some septa, no fungal organisms were detected on special stain, no evidence of tuberculosis, sarcoidosis, or broncho-alveolar carcinoma. Immunochemistry showed predominance of lymphocytes with T-cell and sparse representation of B-cell, no evidence of a monoclonal proliferation to suggest transformation to lymphoma. Lung biopsy culture for bacterial, fungal and mycobacteria were sterile. A diagnosis of lymphocytic interstitial pneumonia was made. He was started on oral prednisolone 40 mg daily along with tab N-Acetylcysteine 600 mg three times daily. Prednisolone was tapered by 10 mg every 2 weeks. Over the following 3 months patient's symptoms improved with decrease in crackles and reduction in the extent of nodularity and ground glass opacification, with improved lung function, so continued on prednisolone 10 mg daily for 6 months, and N-Acetylcysteine 600 mg twice daily. On routine follow-up after 6 months he was asymptomatic with complete clearance on chest and radiological examination, [Figure 4] although HRCT scan chest [Figure 5] showed regression with ill-defined patchy nodules within right middle lobe and superior lingual segment of left lung, so steroids were further reduced. On subsequent follow-up he remained asymptomatic with normal chest examination and normal lung function. Presently he is maintaining on oral prednisolone 5 mg alternate day, doing his normal activity with no symptoms and complete clearance on chest and radiological examination with normal lung function; however, HRCT chest scan revealed regression with reduced nodularity in comparison to last studies.

## DISCUSSION

Lymphocytic interstitial pneumonia is a benign lympho-proliferative disorder of lung characterized by

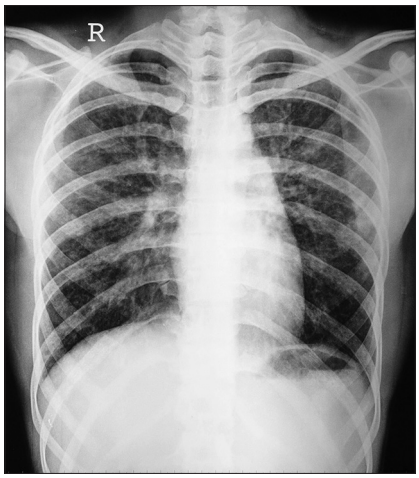


**Figure 1:** Chest radiograph showed bilateral extensive haziness and reticulation

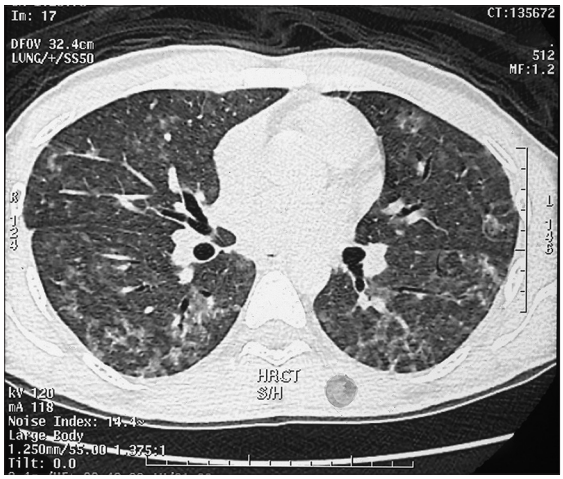


**Figure 2:** Computed tomographic scan of chest revealed ill-defined patchy ground glass densities predominantly in bilateral lower lobes more in the periphery with peribronchovascular interstitial thickening and fissure irregularities, mediastinal lymphnodes enlargement not seen

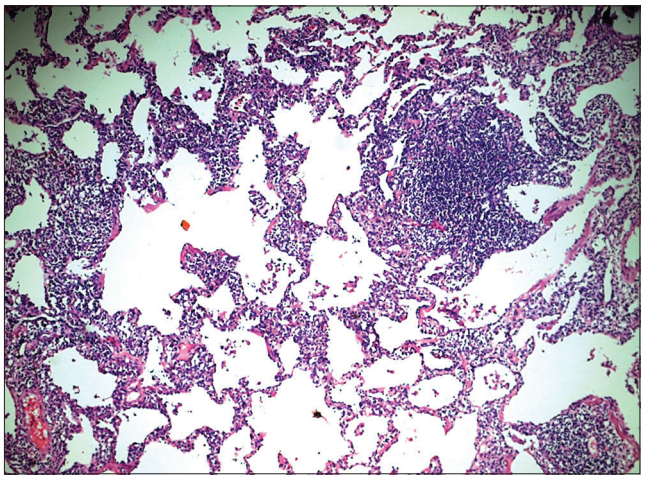

**Figure 3:** H and E, ×20 the alveoli are compressed due to presence of lymphoid aggregates adjacent to the septae

lymphocyte predominant infiltration of interstitium of lung.[6] It is one of the sub-type of interstitial lung disease. It is usually associated with systemic conditions or autoimmune diseases; however, few cases are idiopathic in nature.

Interstitial lung disease is a heterogenous group of more than 200 diseases of various etiologies, of common clinical, radiological and histological features, characterized by diffuse parenchymal involvement either as the (a) primary condition (Idiopathic-IIPs) when the cause is not known and (b) Secondary when the cause is known. ILD is further classified into two groups based on underlying pathology: (1) those associated with predominant inflammation or fibrosis (DPLD) including connective tissue diseases, hypersensitivity pneumonia, infections, toxins, pneumoconiosis, LAM, etc., and (2) those associated with granulomatous reaction e.g. sarcoidosis.

Recently ATS/ERS[1] have revised the classification of IIPs in 2013 and LIP falls under rare entity. As per this classification IIPs are divided into three groups: (a) Major idiopathic interstitial pneumonia, (b) Rare idiopathic interstitial pneumonia and (c) Unclassified idiopathic interstitial pneumonia.

Major IIPs are grouped into (1) Chronic fibrosing IIPs includes idiopathic pulmonary fibrosis- IPF and non-specific interstitial pneumonia -NSIP. (2) Smoking-related IIPs (Respiratory bronchiolitis interstitial lung disease; RBILD) and desquamative interstitial pneumonia (DIP). (3) Acute/subacute idiopathic interstitial pneumonia (Cryptogenic organizing pneumonia; COP). (4) Acute interstitial pneumonia (AIP).

Rare idiopathic interstitial pneumonia: Includes (1) Idiopathic lymphoid interstitial pneumonia-LIP and (2) Idiopathic Pleuro-parenchymal Fibroelastosis.

One of the important diagnostic requirement for IIPs is to exclude known causes of interstitial lung disease like collagen vascular diseases, hypersensitivity pneumonia, environmental exposure and drugs, etc., few cases are idiopathic. LIP is the rare form of IIPs mostly affects women in the 5$^{th}$ decade of life; however, it can occur at any age. Of the known causes LIP is reported to be associated with some systemic and autoimmune diseases such as Sjogren's syndrome (10%),[7] Systemic lupus erythmatosus and rheumatoid arthritis,[8] myasthenia gravis. Infectious diseases such as human immunodeficiency virus infection[9,10] (30-50% of children with HIV/AIDS are affected), EBV virus infection. Other causes includes chronic liver disease, primary biliary diseases, various immunodeficiency diseases, common variable immunodeficiency syndrome,[11,12] and dysproteinemia.[3,6] The patient usually presents with gradual onset of dry cough which is persistent and progressive with increasing breathlessness, constitutional symptoms such as fever, arthralgia, weight loss may be present, hemoptysis, chest pain clubbing usually not present, chest examination reveals bilateral basal crackles,[1,3] manifestations of associated disease may be present. Physical findings may vary in adult and children. Dysproteinemia[3,6] sometimes with increase in IgG, IgM may be present in about in 75% of patients. Chest X-ray shows an alveolar pattern predominantly at the bases from interstitial reticular opacities to nodular opacities,[11,12] with extensive fibrosis and honey combing in advance stage. HRCT[13,14] chest shows areas of ground glass appearance, poorly defined centrilobular nodules, cystic air spaces (honey combing) with interlobular septal thickening and thickening of bronchovascular bundles. BAL shows lymphocytes predominance and pulmonary function test shows a restrictive pattern. Histopathological examination reveals a dense and diffuse interstitial lymphoid infiltrate consisting of lymphocytes, plasma cells and histiocytes.[13] The alveolar septa are extensively infiltrated with cellular infiltrates, lymphoid follicles, germinal and giant cell histiocytes

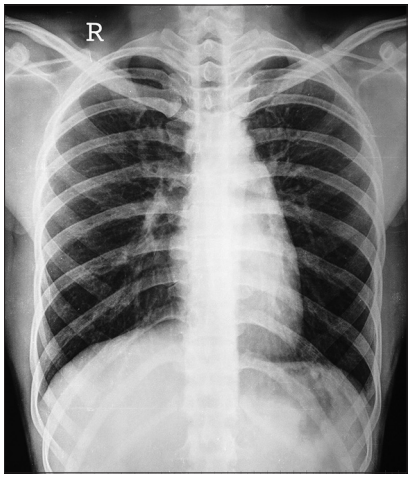


**Figure 4:** Chest radiograph showed complete clearance

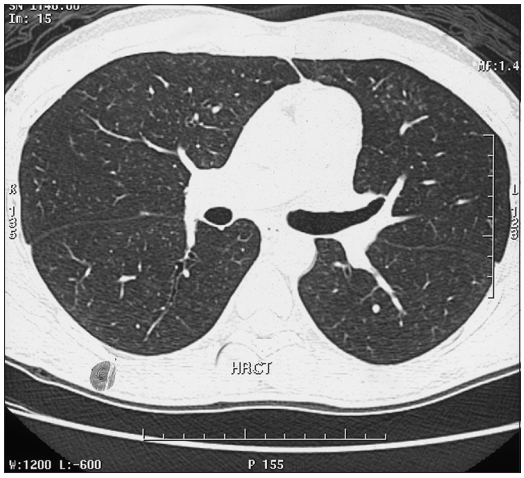


**Figure 5:** HRCT scan chest showed regression with ill-defined patchy nodules within right middle lobe and superior lingual segment of left lung)

may also be seen. Non-necrotizing granulomas and honeycombing may be seen. There is lack of tracking along lymphatic routes which is characteristic of lymphomas, absence of monoclonality on immunohistochemistry for light chains, there is no pleural and lymph nodes involvement, absent organizing pneumonia. Diagnosis of LIP is made on clinical and radiological findings, which is confirmed on lung biopsy and subsequent histological examination. The differential diagnosis of LIP includes NSIP, hypersensitivity pneumonitis, UIP, COP, lymphoma (of mucosa-associated lymphoid tissue-MALT), diffuse lymphoid hyperplasia (hyperplasia of bronchial mucosa-associated lymphoid tissue), *P. jirovecii* pneumonia and other fungal and mycobacterial infection. (1) Hypersensitivity pneumonitis[15,16] have less inflammation contains mixed mononuclear cell infiltrate, small lymphocytes, a peribronchiolar distribution, poorly formed granulomas and intraluminal fibrosis. C.T.[14,16] shows areas of ground glass attenuation and small centrilobular nodules, mosaic air trapping and usually upper lobe distribution. Cystic air spaces, interlobar septal thickening of bronchovascular bundles are not seen. History of exposure and specific IgG antibodies should be considered in such patients (2) NSIP:[17,18] Occurs both as idiopathic and in some diseases such as CVD, drug toxicity, and patients with familial pulmonary fibrosis. It occurs between 50 and 60 years, no gender predominance, not related with smoking, gradual onset, constitutional symptoms may present. The most common HRCT[13] abnormality is bilateral ground glass opacity, linear opacities with traction bronchiectasis. Honeycombing is absent or less evident with sub-pleural sparing. Histopathological feature is characterized by "temporal homogenecity". NSIP has got three major subgroups based on inflammation or fibrosis.(a) Group -1 Cellular NSIP characterized with interstitial inflammation consisting of lymphocytes and plasma cells with no fibrosis.(b) Group 2 characterized by both inflammation and fibrosis.(c) Group-3 Fibrotic NSIP primary with interstitial fibrosis comprising mature collagen and few fibroblast, there is lack of alveolar remodelling with honeycomb cyst formation and active fibroblastic foci which distinguish it from UIP. (3) COP: Presented as flu-like illness, few physical findings, affected middle-aged person no gender predilection, not associated with smoking, chest X-ray shows patchy migratory unilateral or bilateral consolidation. C.T. chest shows subpleural/peribronchial patchy consolidation and nodules predominantly in lower lobes. Histologically there is organising pneumonia consisting of polyps with alveolar ducts and alveoli, interstitial inflammatory infiltrate/ intra-alveolar foamy macrophages, preservation of lung architecture, centred on small airways. Other diseases like *P. jerovecii*, mycobacterial and other fungal infection should be excluded by culture of the organism. Although LIP is steroids responsive treatment is quite variable with some patients improve completely, while others responds poorly and may require immunosuppressive therapy. Steroids are used for long time to achieve complete remission, in addition immunosuppressive agents like methotraxate, azathioprine or chlorombucin may be required in view of blood gas analysis and hypoxia. The index case who was diagnosed to have lymphocytic interstitial pneumonia treated successfully with steroids with complete clearance on chest and radiological examination and no symptoms after 6 months after starting steroids, therefore kept on a minimum dose of steroids. Presently patient is asymptomatic, with complete clearance on chest and radiological examination with normal pulmonary function test.

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