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Connective tissue disease interstitial lung disease with high concentration of Krebs von den lunge 6: A case report

Dewi Sari[1,2*], Fariz Nurwidya[2,3], Betty Agustina Tambunan[4,5]

[1]*Clinical Pathology sub-Specialization Programme, Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga- Surabaya, Indonesia*
[2]*Persahabatan National Hospital, Jakarta, Indonesia*
[3]*Departement of Pulmonology, Faculty of Medicine Universitas Indonesia*
[4]*Department of Clinical Pathology, faculty of medicine, Universitas Airlangga, Surabaya, Indonesia*
[5]*Department of Clinical Pathology, Dr. Soetomo General Academic Hospital, Surabaya Indonesia*

Abstract

Background and Clinical Significance: Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD) is a collection of systemic autoimmune disorders resulting in lung interstitial abnormalities or lung fibrosis. CTD - ILD pathogenesis is not well characterized because of disease heterogeneity; Case Presentation: A 67 years old female presented to the hospital through outpatient clinic with dyspnea for almost 3 – 4 months, patient underwent DLCO, HRCT and blood test such as ANA IF, RF, ANA profile, Myositis panel and KL-6 and diagnosed CTD-ILD based on findings. Patient has positive ANA IF, positive Ro-52, and PL-12 autoantibody also high concentration of KL-6 which is suggestive to CTD-ILD. HRCT result also support CTD – ILD with indeterminate UIP pattern; Conclusions: HRCT is one of gold standard in establishing diagnosis of CTD-ILD and KL-6 can help early detection and diagnosis of CTD-ILD.

Keywords: CTD-ILD; HRCT; KL-6

Introduction

Connective Tissue Diseases are systemic autoimmune disorders caused by excessive immune activated inflammation that targets the connective tissues of the body as seen in Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Sjogren's syndrome (SS), idiopathic inflammatory myopathies such as dermatomyositis (DM) and polymyositis (PM), Systemic Sclerosis (SSc), and Mixed Connective Tissue Disease (MCTD). Interstitial Lung Disease exists in approximately 40–50% of patients with CTDs, and is the main cause of morbidity and mortality.[Fischer and Du Bois, 2012; Avendano-Mira et al, 2019] Lung fibrosis occurs in approximately four-fifths of patients with SSc, approximately one-fourth develop progressive Interstitial Lung Disease (ILD), with 10-year mortality of around 40% making it one of the leading causes of morbidity and mortality.[Perelas et al 2020; Khanna et al 2020] ILD is a rare disease with an estimated number of 3–24 patients per 100,000 people. [Avendano-Mira et al, 2019]

Early diagnosis of CTD-ILD is crucial to initiate treatment and prevent disease progression, thus, High-resolution computed tomography (HRCT) of the chest is recognized as a modality of choice for diagnosing and assessing CTD-ILD. Further, the latter demands familiarity with HRCT findings and thorough clinical examination. Interstitial Lung Disease is characterized by inflammation and or fibrosis within the alveolar interstitium of the lung. Approximately 30% to 40% of people with ILD develop progressive pulmonary fibrosis, which typically causes resporatory failure. [Fischer and Du Bois, 2012; Hamid et al., 2019]

Interstitial Lung Disease (ILD) represents one of the most severe and potentially life-threatening manifestations of Sjögren's syndrome, although its clinical presentation can vary widely among patients. The presence of pulmonary involvement in individuals with Sjögren's syndrome often remains subclinical for a prolonged period, with subtle or absent respiratory symptoms in the early stages. Consequently, ILD may only be detected incidentally or after significant structural lung damage has already occurred. This underscores the importance of active and systematic screening for pulmonary involvement in all patients with Sjögren's syndrome,

Correspondence: Dewi Sari, Clinical pathology sub-Specialization programme, Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga-Surabaya, Indonesia, **e-mail:** betty-a-t@fk.unair.ac.id, **Received:** September 29, 2025 **Accepted:** November 12, 2025

even in the absence of respiratory complaints. In this context, serological biomarkers offer a promising approach as low-cost, radiation-free, and easily repeatable tools for the early detection and longitudinal monitoring of ILD, complementing imaging and pulmonary function testing.

Among these biomarkers, Krebs von den Lungen-6 (KL-6) has emerged as one of the most useful and well-validated indicators of interstitial lung involvement. KL-6 is a high–molecular-weight mucin-like glycoprotein expressed on the surface of type II alveolar pneumocytes and other epithelial cells. Under normal conditions, KL-6 expression is limited; however, during alveolar epithelial injury or regeneration, type II pneumocytes markedly upregulate KL-6 production, leading to its elevated release into the bloodstream. Consequently, increased serum KL-6 concentrations reflect ongoing alveolar epithelial damage, inflammation, and fibrotic remodeling within the lung parenchyma. Since 1999, the Japanese National Health Insurance system has officially recognized and reimbursed KL-6 measurement as a diagnostic and monitoring biomarker for interstitial lung diseases, highlighting its clinical value and reliability in daily practice [Kohno et al., 1993; Meyer, 2014; Kashmeeri et al., 2021].

Case presentation

A 67-year-old female presented to our hospital's outpatient pulmonary clinic with a progressive history of dyspnea that had persisted for approximately three to four months prior to admission. The shortness of breath was gradual in onset and had progressively worsened over time, particularly during physical exertion such as walking or performing household activities. The patient also reported an unproductive, persistent cough that was not associated with chest pain, hemoptysis, or wheezing. There were no constitutional symptoms such as fever, weight loss, or night sweats. In reviewing her medical history, the patient mentioned that over the past three years, she had experienced intermittent numbness and tingling sensations in both feet, suggestive of possible peripheral neuropathy, though she had not sought neurological evaluation. Importantly, she denied sicca symptoms, including dryness of the eyes (xerophthalmia) or mouth (xerostomia), which are commonly associated with connective tissue diseases such as Sjögren's syndrome. Regarding her environmental and occupational background, the patient reported a history of chronic passive cigarette smoke exposure for approximately 10–15 years, as her spouse was a regular smoker at home. However, she herself had never smoked. She was employed for many years in the restaurant service industry, where she primarily worked in food preparation and customer service areas. She denied any direct or occupational exposure to known respiratory irritants, such as industrial dust, chemical fumes, or asbestos. Her medication history was unremarkable; there was no prior long-term use of any prescription drugs, including corticosteroids or immunosuppressants. The patient stated that previous treatments were limited to symptomatic therapy for minor ailments such as cough or upper respiratory tract infections. Additionally, she had a documented history of hospitalization for pneumonia, although complete details regarding the etiology and management of that episode were not available. At the time of presentation, there was no reported history of autoimmune diseases, connective tissue disorders, or other chronic systemic illnesses in the patient or her family.

On general physical inspection, there were no remarkable findings. The patient appeared well-nourished and in no acute distress. There were no signs of digital clubbing, cyanosis, or peripheral edema. Examination of the skin revealed no abnormal pigmentation, rashes, telangiectasia, or sclerodermatous changes. The nail beds and fingertips were normal in appearance, and there were no ulcerations or Raynaud's phenomenon observed during examination. On chest examination, vesicular breath sounds were heard bilaterally with no rhonchi or wheezing. However, fine late-inspiratory crackles were appreciated in both lung fields, suggesting the presence of interstitial involvement. The remainder of the physical examination was unremarkable.

Spirometry performed on August 7, 2025, showed a Vital Capacity (VC) of 1110 mL (108% predicted), a Forced Vital Capacity (FVC) of 1026 mL (100% predicted), and a Forced Expiratory Volume in one second (FEV_1) of 706 mL (132% predicted). The FEV_1/FVC ratio was 90%, indicating normal airflow. The diffusing capacity for carbon monoxide (DLCO)

was mildly reduced at 67% of predicted value.

This test showed that no restriction, no obstruction and Diffusing capacity of the lung for carbon monoxide (DLCO) test result showed mildly reduced diffusing capacity (67%). A follow-up HRCT of the thorax performed on April 10, 2025, was compared with the previous non-contrast chest CT obtained on December 16, 2024. The current examination revealed multiple nodules in segment 1 of the right lung, as well as calcified nodules in segment 3 of the right lung measuring approximately 0.3–0.9 cm in diameter (previously 0.2–1.4 cm). Areas of fibrosis, consolidation, and ground-glass opacities (GGO) were observed in segments 2–10 of the right lung, predominantly distributed in the subpleural and basal regions, accompanied by reticular abnormalities. Bronchiectasis was noted in segment 10 of the right lung. In the left lung, fibrosis and GGO with reticular abnormalities were observed throughout all segments, with a predominant subpleural, basal, and peribronchovascular distribution. Bronchiectasis was also seen in segments 9 and 10 of the left lung, along with fibrotic changes in segments 4 and 5. The overall findings were suggestive of an indeterminate Usual Interstitial Pneumonia (UIP) pattern, with Differential Diagnosis including Desquamative Interstitial Pneumonia (DIP), as areas of consolidation and GGO showed partial regression compared to the previous examination. Cardiomegaly with aortic calcification and elongation was also noted.

Comprehensive laboratory investigations were performed in this patient. The antinuclear antibody (ANA) immunofluorescence assay (ANA-IF) revealed a positive result with a cytoplasmic speckled pattern at a titer of 1:100, while the rheumatoid factor was negative. Further serological testing, including an ANA profile and myositis antibody panel, was subsequently performed to identify specific autoantibodies. The ANA profile demonstrated the presence of Ro-52 autoantibody, a finding commonly associated with connective tissue diseases such as Systemic Lupus Erythematosus (SLE), Systemic Sclerosis, and Sjögren's syndrome. These serological results supported the suspicion of autoimmune-mediated interstitial lung disease in this patient.

The myositis antibody panel was performed using the Euroline Autoimmune Inflammatory Myopathies 16 Ag, cN-1A, and HMGCR assay (Euroimmun, Germany). The test revealed the presence of PL-12 and Ro-52 autoantibodies. The detection of PL-12, an anti–aminoacyl-tRNA synthetase antibody, is strongly associated with the antisynthetase syndrome and interstitial lung disease, while the presence of Ro-52 is frequently observed in patients with Systemic Lupus Erythematosus (SLE), Systemic Sclerosis, Sjögren's Syndrome, and Polymyositis. Taken together, these serological findings indicate an overlap autoimmune process involving features of connective tissue disease and inflammatory myopathy, consistent with connective tissue disease–associated interstitial lung disease (CTD-ILD) (Figure 1).

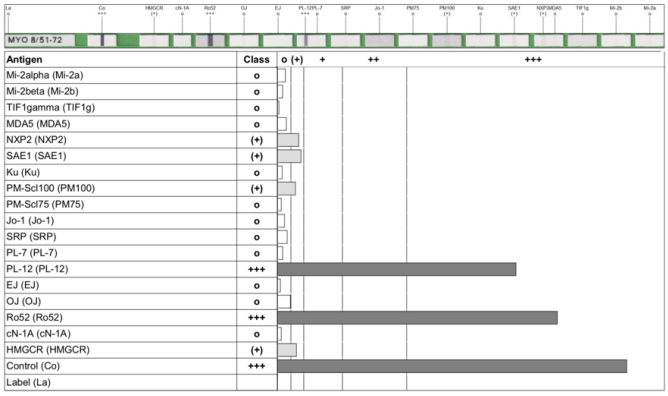

Figure 1. Myositis panel result

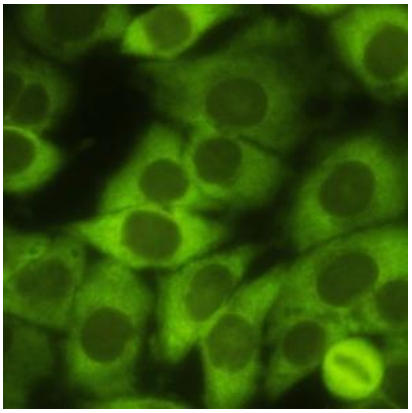

Figure 2. ANA IF: Cytoplasmic speckled

We also performed a serum Krebs von den Lungen-6 (KL-6) measurement in this patient as part of the diagnostic and monitoring workup for Interstitial Lung Disease (ILD) associated with connective tissue disease. The quantitative analysis of KL-6 was carried out using the Nanopia KL-6 assay (Sekisui Medical

Co., Tokyo, Japan), which is a latex agglutination immunoassay performed on the Abbott Alinity c analyzer (Abbott Diagnostics, USA). In this method, KL-6 molecules present in the patient's serum react specifically with mouse monoclonal anti–KL-6 antibody–coated latex particles, forming antigen–antibody complexes that cause visible agglutination. The degree of this agglutination is then measured photometrically as a change in absorbance, which directly correlates with the KL-6 concentration in the sample. The assay provides a rapid, quantitative, and highly reproducible measurement suitable for routine clinical application. To ensure analytical reliability and result validation, the KL-6 concentration was also assessed using an alternative method, the Fluorescence Immunoassay (FIA) technique, employing the AFIAS KL-6 kit (Boditech Med Inc., Republic of Korea). This method detects KL-6 through fluorescence signal intensity generated by antigen–antibody binding, providing an additional layer of confirmation. Both assays were performed in strict accordance with the manufacturers' protocols, with a reference cut-off value of 500 U/mL recommended for the identification of elevated KL-6 levels indicative of ILD activity. In this patient, the serum KL-6 concentration measured 3188.5 U/mL using the Nanopia KL-6 assay and was reported as greater than 3000 U/mL using the AFIAS method. These values were markedly above the established reference threshold and therefore strongly suggestive of active interstitial lung involvement, consistent with the patient's radiologic findings and clinical presentation. The elevated KL-6 levels further supported the diagnosis of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD) and served as an important biochemical indicator of ongoing pulmonary epithelial injury and fibrotic activity.

The patient was managed with a combination of immunosuppressive, supportive, and symptomatic therapies. The prescribed medications included Myfortic (mycophenolic acid) 360 mg twice daily as a maintenance immunosuppressant to control autoimmune activity and prevent further progression of interstitial lung involvement; vitamin D 5000 IU once daily to support bone health and immune modulation; lansoprazole 30 mg once daily as gastric protection during long-term immunosuppressive therapy; and codeine 10 mg three times daily for symptomatic relief of persistent cough associated with interstitial lung disease.

The patient was closely monitored through regular outpatient visits every 4–6 weeks to evaluate clinical progress and treatment tolerance. Serial physical examinations showed gradual improvement in respiratory symptoms, with a noticeable reduction in the frequency and severity of cough and mild improvement in exertional dyspnea. No significant adverse effects related to Myfortic or other prescribed medications were observed during follow-up.

Discussion

Interstitial Lung Disease (ILD) associated with Connective Tissue Disease (CTD) represents a distinct subset of ILD in which autoimmune mechanisms play a crucial role in disease development and progression. The presence of ILD can significantly impact morbidity and mortality among patients with CTD, emphasizing the importance of early recognition and diagnosis. Our patient presented with acute exacerbation of symptoms of Connective tissue disease - Interstitial Lung Disease (CTD-ILD). DLCO test result showed mildly reduced diffusing capacity (67%) indicated impaired gas exchange due to interstitial involvement along with HRCT that is suggestive of indeterminate usual interstitial Pneumonia pattern (UIP). The HRCT findings demonstrated progressive fibrotic changes with a subpleural and basal predominance, accompanied by reticulation, bronchiectasis, and areas of residual ground-glass opacities. These imaging features were consistent with an Interstitial Lung Disease (ILD) pattern. The indeterminate Usual Interstitial Pneumonia (UIP) pattern raised the possibility of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD). The presence of basal fibrosis and traction bronchiectasis, along with partial resolution of consolidation and GGO compared to the previous scan, suggested an ongoing but partially responsive inflammatory process. The differential diagnosis of Desquamative Interstitial Pneumonia (DIP) was also considered, given the history of long-term passive smoke exposure. Cardiomegaly with aortic calcification and elongation was noted as a concurrent finding, possibly related to chronic systemic inflammation or age-related vascular changes.

HRCT which is considered the most sensitive and gold standard modality in the diagnosis of CTD-ILD and has the utmost importance in monitoring disease prognosis. Despite established guidelines to use HRCT some of disadvantages such as lack of clinical experience, adequate knowledge, radiation exposure, imaging cost, and feasibility may be among the factors in its hindrance. That is the reason we try to use KL-6 assay in our patient; KL-6 is a high molecular weight glycoprotein found on the surface of diverse epithelial cell types. The surface expression of KL-6 is induced during the regeneration process of type II pneumocytes, resulting in an increased concentration in serum. KL-6 concentration using Nanopia and AFIAS are 3188.5 U/mL and more than 3000 U/mL respectively which is suggestive ILD. Cho et al, found that The average KL-6 concentration in CTD-ILD patients was significantly higher than that in the healthy control groups (685,3 ±566.3 U/mL vs 168.4 ± 62.4 U/mL).[8] KL-6 measured using Nanopia with automated analyser makes clinical laboratories can perform KL-6 assay, faster and more convenient and can help clinician to give better treatment while waiting for HRCT result (Cho et al, 2019). Several studies have demonstrated that serum KL-6 levels correlate with the severity and extent of interstitial involvement observed on high-Resolution Computed Tomography (HRCT), as well as with pulmonary function parameters such as DLCO. Elevated KL-6 levels have also been associated with disease progression and poorer prognosis in patients with Connective Tissue Disease–Associated ILD (CTD-ILD) And Idiopathic Interstitial pneumonias. In CTD-associated ILD, KL-6 can serve as a non-invasive marker to assess treatment response and disease activity. The patient's high KL-6 value, in combination with HRCT findings and positive autoimmune serology (PL-12 and Ro-52 antibodies), strongly supports the diagnosis of autoimmune-related interstitial lung disease. Serial monitoring of KL-6 levels during follow-up may help evaluate therapeutic response to immunosuppressive therapy and detect potential relapse or progression. The markedly elevated KL-6 concentration in this case reflects active alveolar injury and ongoing fibrotic remodeling, consistent with the HRCT and DLCO findings. Previous studies have demonstrated that patients with persistently high KL-6 levels tend to experience more rapid ILD progression and poorer pulmonary outcomes. Thus, KL-6 can serve not only as a diagnostic marker but also as a dynamic biomarker for disease monitoring. In clinical practice, serial measurement of KL-6 may help evaluate treatment response and detect early relapse during follow-up, particularly when radiological or spirometric changes are subtle.

First-line immunological testing for the screening of CTD-ILD patients should always include antinuclear antibodies (ANA), ANA profile, and rheumatoid factor (RF Connective tissue disease in this patient was diagnosed using positive ANA IF (titter 1:100), positive Ro-52 and PL-12 autoantibody using ANA profile pattern and myositis panel which suggest Systemic Lupus Erythematosus, Systemic Sclerosis, Sjorgen syndrome and Poymyositis. Autoantibody testing provided key diagnostic information. The patient showed positive ANA with a cytoplasmic speckled pattern and the presence of Ro-52 and PL-12 autoantibodies. The coexistence of these antibodies is often associated with autoimmune inflammatory myopathies, particularly **antisynthetase syndrome**, which may manifest as ILD, myositis, arthritis, Raynaud's phenomenon, and mechanic's hands. However, in some cases, ILD may precede or even occur without overt muscle involvement, as seen in this patient. Ro-52 positivity has been reported in several autoimmune conditions such as systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome, and is also linked to more severe or treatment-resistant forms of ILD. Meanwhile, PL-12 (anti-alanyl-tRNA synthetase) is one of the antisynthetase antibodies strongly associated with ILD, often with minimal or absent myositis features, referred to as "clinically amyopathic antisynthetase syndrome. Immunological evaluation revealed a positive ANA immunofluorescence assay with a cytoplasmic speckled pattern (titer 1:100) and a negative rheumatoid factor, suggesting the presence of a non-rheumatoid autoimmune process.

Ro-52 autoantibody has been linked to the development and progression of Interstitial Lung Disease (ILD), particularly in patients with connective tissue disorders. Its presence has been associated with increased risk of pulmonary fibrosis and poorer respiratory outcomes, even in patients without overt systemic manifestations. In this case, the combination of positive Ro-52 antibody, mild diffusion impairment, and radiological evidence of interstitial changes supports the diagnosis of

connective tissue disease–associated ILD.

The patient was treated with Myfortic (mycophenolic acid) 360 mg twice daily as an immunosuppressive agent to suppress autoimmune activity and prevent further progression of Interstitial Lung Disease (ILD) secondary to Connective Tissue Disease (CTD). The choice of mycophenolic acid was based on its established efficacy and favorable safety profile in managing CTD-associated ILD, particularly in patients with systemic lupus erythematosus and other autoimmune-related pulmonary manifestations. In addition, vitamin D 5000 IU once daily was administered to maintain bone mineral density and modulate immune function, given the increased risk of vitamin D deficiency and osteoporosis in patients undergoing long-term immunosuppressive therapy.

To minimize gastrointestinal side effects related to chronic immunosuppressant or corticosteroid use, lansoprazole 30 mg once daily was prescribed as a proton pump inhibitor for gastric mucosal protection and the prevention of peptic ulcer disease. For symptomatic management, codeine 10 mg three times daily was given to alleviate the patient's persistent non-productive cough associated with interstitial lung involvement, thereby improving overall comfort and quality of life. The treatment regimen was continued with regular clinical follow-up, laboratory evaluation, and monitoring of pulmonary function and KL-6 levels to assess therapeutic response and detect potential adverse effects at an early stage.

Conclusions

A 67-year-old female is diagnosed with Connective Tissue Disease - Interstitial Lung Disease (CTD-ILD). The gold standard non-invasive diagnosis can be made with HRCT which can record even the early changes. Early detection and easier examination using KL- 6 can give prompt management to prevent morbidity and mortality. The clinical, radiological, and serological findings in this case collectively support the diagnosis of Connective Tissue Disease–Associated Interstitial Lung Disease (CTD-ILD). The markedly elevated KL-6 level provides additional evidence of active alveolar injury and ongoing fibrotic activity within the lungs. Considering its strong correlation with disease activity and prognosis, KL-6 represents a valuable biomarker for both the diagnosis and longitudinal monitoring of ILD in autoimmune conditions. Regular assessment of KL-6 levels, in conjunction with pulmonary function testing and HRCT evaluation, may therefore aid in early detection of disease progression and in guiding timely therapeutic interventions. Early recognition and close follow-up of KL-6 dynamics could contribute to improved clinical outcomes and prevention of irreversible pulmonary fibrosis in patients with CTD-ILD.

Informed Consent Statement

"Written informed consent has been obtained from the patient(s) to publish this paper"

Conflicts Of Interest

"The authors declare no conflicts of interest."

Abbreviations

The following abbreviations are used in this manuscript:

ANA-IF	**Anti-Nuclear Antibody scence**
CTD-ILD	Connective tissue disease-associated disease
DLCO	Diffusing capacity of the lung for carbon
DM	Dermatomyositis
HRCT	High-resolution computed tomography
KL-6	Krebs von den Lungen 6
MCTD	mixed connective tissue disease
PM	Polymyositis
SLE	Systemic Lupus Erythematosus
SS	Sjogren's syndrome
SSc	Systemic Sclerosis
UIP	usual interstitial Pneumonia

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