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CASE REPORT ARTICLE

# Interstitial Lung Disease in Rheumatoid Arthritis: A Clinical Dilemma

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## Abstract

Rheumatoid arthritis (RA)–associated interstitial lung disease (RA-ILD) is an increasingly common extra-articular cause of mortality and morbidity in RA. Here, we present the case of an 82-year-old female suffering from RA-ILD. She presented with a 20-year history of RA with new-onset progressively worsening dyspnoea, pyrexia, and dry cough, which were not responsive to initial antibiotics. Moreover, she had been on long-term methotrexate, which can cause pulmonary disease. Investigations revealed raised inflammatory markers, restrictive lung patterns, and radiological features of ILD. She was treated with a tapering course of oral prednisolone and home oxygen, which provided some symptomatic improvement. Diagnosis of RA-ILD can be challenging due to several contributing factors. Optimal treatment is controversial, and corticosteroids have been widely used but with limited effects. There is evidence directed at potential therapeutic benefit from a number of newer agents, which are discussed.



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# Interstitial Lung Disease in Rheumatoid Arthritis: A Clinical Dilemma

## Introduction

It is estimated that nearly half of patients with rheumatoid arthritis (RA) will develop some form of associated respiratory complication in their lifetime.[1] Of these, interstitial lung disease (ILD), characterized by inflammation, scarring, and fibrosis of lung tissue, is the only complication of RA with an increasing prevalence, accounting for about 7% of deaths in early RA.[2-3] Moreover, the medications used in treating RA can cause respiratory toxicity and this can complicate diagnosis. Despite several recent promising developments, the understanding of RA-ILD is not well established and its management has not been clearly defined. In light of this, we report a case of RA-ILD that presents a clinical dilemma.

## Case Summary

An 82-year-old female presented with a 2-week history of new-onset progressively worsening dyspnoea (both on physical exertion and at rest), pyrexia (37.8°C), and dry cough.

She was initially treated for community-acquired pneumonia with antibiotics (amoxicillin and clarithromycin 500 mg) but without symptomatic improvement. Moreover, she had been taking 15 mg of methotrexate once weekly for 15 years, which was subsequently stopped. She has no known drug allergies and is also on regular prescriptions of folic acid, calcium tablets, naproxen, and alendronate sodium for her musculoskeletal problems – long-standing seropositive RA (20 years), osteoarthritis, and osteoporosis – which have been well controlled. She is a non-smoker and is normally mobile and active without any known respiratory problems. There were no previous exposures to asbestos or industrial chemicals but she kept cockatiels at home for years. On clinical examination, lower lobes of the lungs were dull on percussion and bilateral inspiratory basal crackles were heard on auscultation with decreased air entry into both lower lobes. Her respiratory rate was 28 breaths/minute. Rheumatoid changes were also noted on her hands but without any digital clubbing.

Laboratory workup revealed the following:

- Haemoglobin – 11.1 g/dL (↓)
- White cell count – 16.2 × $10^9$/L (↑) (no evidence of eosinophillia)
- Platelets – 425 × $10^9$/L (↑)
- INR – 1.4 (↑)
- C-reactive protein –156.9 mg/L (↑).
- Arterial blood gases –
  - pH=7.509 (↑),
  - $PO_2$=6.69 kPa (↓)
  - $PCO_2$=4.7 kPa
  - $HCO_3^-$=28.2 mmol/L
  - Base excess = 4.5 mmol/L (↑)

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In addition, her pulmonary function tests (PFTs) revealed a restrictive pattern, with a reduced diffusing capacity and carbon monoxide transfer coefficient (*K*co). Her oxygen saturation was 78% on room air. A chest radiograph (Figure 1 with white arrows) revealed increased bilateral patchy airspace shadowing as compared to imaging performed 2 years earlier. Additionally, a high-resolution computed tomography (HRCT) scan of the thorax (Figure 2) showed bilateral basal honeycombing with peripheral patchy ground-glass opacification (white arrows) and traction bronchiectasis (black arrows). The overall clinical picture was consistent with interstitial lung disease (pulmonary fibrosis) secondary to either rheumatoid arthritis (RA-ILD) or with possible superimposed methotrexate-induced pneumonitis. Other differential diagnoses considered were aspiration pneumonia, pneumocystis infection, acute exacerbation of an existing ILD, and hypersensitivity pneumonitis (cockatiel exposure).

She was treated with a tapering course of oral prednisolone (20 mg once daily on discharge for 4 weeks, followed by 15 mg, then 10 mg) and 4 L/minute of home oxygen. On latest follow-up, her oxygen saturations improved to 97% on 2 L of oxygen. However, PFT results remained largely unchanged.

**Figure 1. Anteroposterior erect chest X-ray**

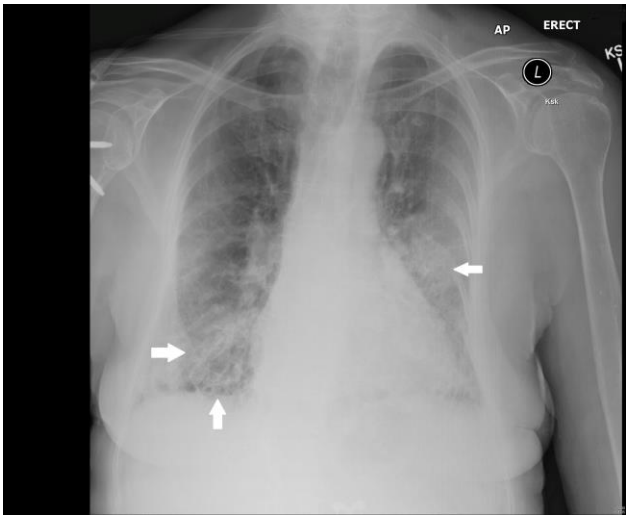
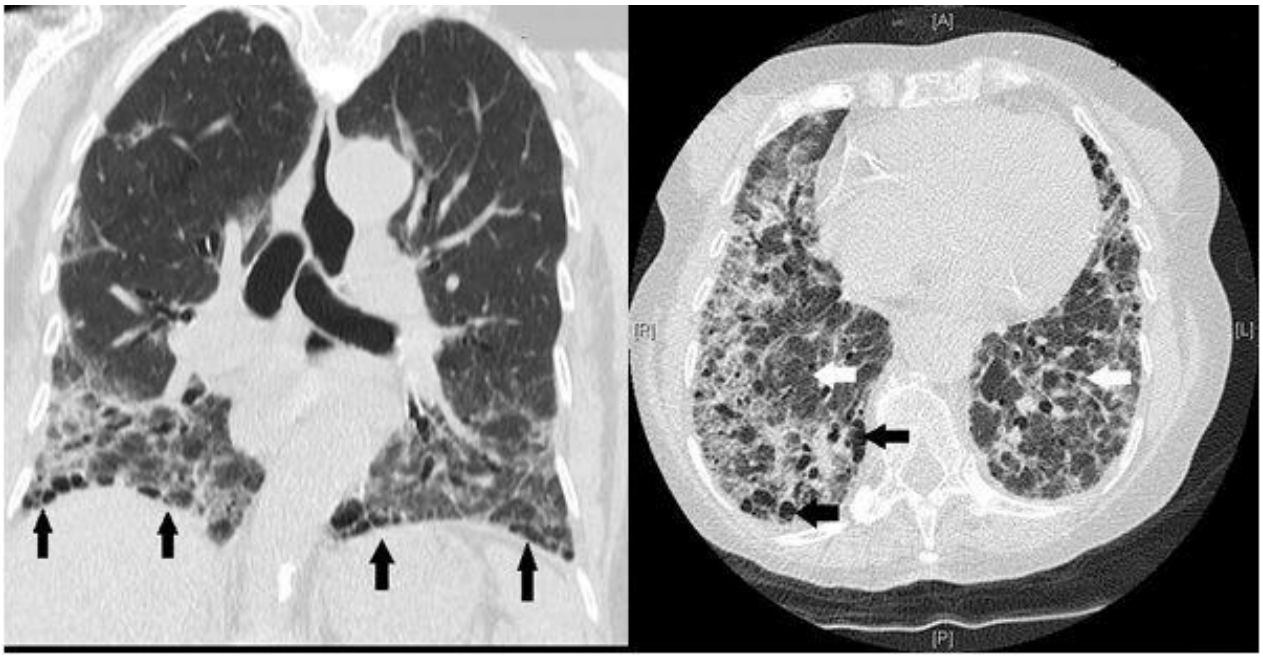


**Figure 2. HRCT scans of the thorax**




## Discussion

*Prevalence and risk factors of RA-ILD*

Despite the high incidence of ILD in patients with RA, not every patient is symptomatic. McDonagh *et al.* revealed that ILD has been diagnosed in around 20–30% of unselected RA populations using HRCT,[4] and about half of these patients present with respiratory symptoms.

The predictors for RA-ILD include smoking,[5-6] male sex,[7] long duration of disease, and the presentation of systemic features such as fever and weight loss.[8] Moreover, increased polymorphisms at the HLA-B40 and HLA-B54 antigen sites have been found in RA-ILD and cryptogenic organizing pneumonia (COP).[9-10] Also, some evidence suggests that patients who are seropositive for rheumatoid factor and/or possess anti–cyclic citrullinated peptide (anti-CCP) antibodies are at risk of developing RA-ILD.[11-13]

*Methotrexate-induced ILD*

Methotrexate, the first-line disease-modifying antirheumatic drug (DMARD) in treating RA, is known to cause methotrexate-induced pulmonary toxicity, of which methotrexate pneumonitis (inflammation of lung tissue) is common,[14] and this can progress to pulmonary fibrosis.[15] The most significant risk factor for developing pneumonitis is pre-existing pulmonary disease, coupled with a baseline diffusing capacity of < 70% predicted, which increases the risk of developing methotrexate drug toxicity 10-

fold.[16] Other risk factors are listed in Table 2.

Lung toxicity often occurs after weeks to months of low-dose oral methotrexate therapy, which has been associated with a possible 20% increased mortality rate if toxicity occurred within first 6 months of treatment.[17] In about 90% of patients with methotrexate-induced pulmonary toxicity, low grade fever has been reported. Also, approximately 80% of patients presented with a dry, non-productive cough and dyspnoea on exertion.[17]

Hence, methotrexate should be carefully considered in patients with prior RA-ILD[18] due to the increased susceptibility of developing pneumonitis, even though methotrexate does not directly exacerbate ILD.[19] Table 1 lists the criteria for diagnosis methotrexate pneumonitis.

**Table 1: Criteria for diagnosis of methotrexate-pneumonitis by Searles and McKendry[22]**

| | |
|---|---|
| **1.** | **Acute- onset dyspnea** |
| **2.** | **Fever > 38° C** |
| **3.** | **Tachypnoea ≥ 28 breaths/minute, and dry cough** |
| **4.** | **Radiological evidence of pulmonary interstitial disease or alveolar infiltrates** |
| **5.** | **White blood cell < 15, 000 cells/mm$^3$, with or without eosinophillia** |
| **6.** | **Negative blood and sputum cultures (mandatory)** |
| **7.** | **Restrictive defect and decreased $D_L$CO $D_L$co on PFT** |
| **8.** | **$PO_2$ < 60 mmg Hg on room air** |
| 9. | **Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection** |
| **Definite: > or = if 6 or more criteria met; probable if : 5 of 9 criteria met; possible if: 4 of 9 criteria met** | |

**Table 2: Pulmonary Toxicities Associated with RA medications (Adapted from Hamblin et al[20] & Lake et al[21])**

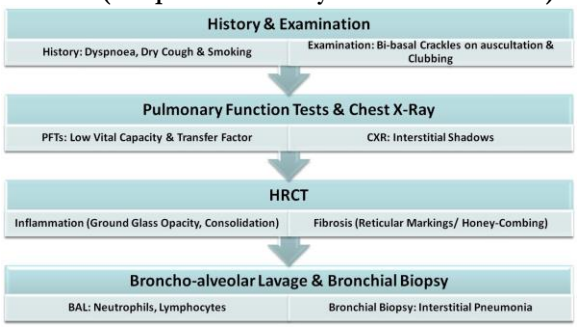
| Drug Class | Pulmonary Toxicity | Risk Factors |
|---|---|---|
| **Anti-Inflammatory inflammatory Drugs** | | |
| **NSAIDs** | Non-cardiogenic pulmonary oedema<br>Acute eosinophillic pneumonia<br>Interstitial Pneumonitis | High-dose treatment |
| **Corticosteroids** | Infection | Dose related<br>Pre-existing severe pulmonary disease<br>Use of biologic DMARDs |
| **Non-Biologic biologic DMARDs** | | |
| **Methotrexate** | Acute interstitial pneumonia<br>Pulmonary fibrosis<br>Pleural thickening<br>Chronic cough | **Major Risk Factors:**<br>Carbon monoxide diffusing capacity of the lung ($D_L$co) < 70% predicted (Increased risk by 10%)<br>Tobacco Abuse > of > 25 pack years<br>Hypoalbuminaemia<br>Previous use of DMARDs<br>**Minor Risk Factors:**<br>RA with pleuropulmonary involvement<br>Advanced Older age<br>Diabetes Mellitus |
| **Leflunomide** | Interstitial Pneumonitis - Acute lung injury and Diffuse alveolar damage<br><br>Nodulosis | Loading dose of leflunomide<br>Pre-existing ground- glass infiltrates on HRCT<br>Previous use of methotrexate<br>Japanese origin |
| **Sulfasalazine** | Eosinophillic pneumonia with peripheral eosinophillia and interstitial inflammation with or without fibrosis<br>Organizing pneumonia (OP)<br>Non-specific interstitial pneumonia (NSIP) | Unknown |
| **Gold Salts (Rarely used)** | Interstitial Pneumonitis<br>Bronchiolitis obliterans with or without organizing pneumonia, pulmonary- renal syndrome<br>Diffuse alveolar damage | Unknown, possible genetic association ( HLA-B40, HLA-A3, HLA-B35, and Dw1 expression) and cumulative ingestion > 500 mg gold |
| **DP-Penicillamine (Rarely used)** | Bronchiolitis obliterans<br>Pulmonary- renal syndrome<br>Diffuse alveolar damage | Unknown |
| **Biologic DMARDs** | | |
| **Anti-TNF-α biologic agents:**<br>**Etanercept (soluble p75 TNF- α receptor fusion protein)**<br>**Infliximab (dimeric anti-TNF- α)**<br>**Adalimumab (anti-TNF- α monoclonal antibody)**<br>**Golimumab**<br>**Certolizumab** | Infection including tuberculosis (pneumonia 0.8%)<br>Pneumonitis (0.6%)<br>o Acute lung injury<br>o Usual interstitial pneumonia (UIP)<br>o Non-specific interstitial pneumonia (NSIP)<br>Non-infectious granulomatous disease<br>New lung nodules | Low body weight<br>Older age<br>Previous MTX methotrexate pneumonitis /lung disease<br>Chest X-ray and Mantoux or QuantiFERON Gold before therapy |
| **Anakinra (IL-1 blocker)** | Infection | Unknown |
| **Rituximab (anti-–B cell monoclonal antibody)** | Organizing pneumonia (Rare)<br>Rapidly progressive pulmonary fibrosis (Rare) | Unknown |
| **Abatacept (selective co-stimulation modulator preventing T-cell CD28 binding)** | Pneumonitis | Unknown |
| **Tocilizumab (humanized anti-–IL-6 receptor monoclonal antibody)** | Rare exacerbation of pre-existing ILD | Pre-existing ILD |

*Diagnosis of ILD*

A thorough clinical evaluation is necessary in RA patients presenting with respiratory symptoms[18] (Figure 3). This is followed by a chest radiograph and PFTs to rule out common respiratory conditions like infection. HRCT of the thorax is the gold-standard investigation[23] which confirms ILD and defines whether it is an extensive disease (involving > 20% of total lung volume) or a limited disease (< 20% of total lung volume).[24-25] As seen in our case, the presence of bibasal ground-glass infiltrates, increased reticular markings, and honeycombing on HRCT is highly indicative of ILD.[26] Other findings may also include pleural involvement, rheumatoid nodules, bronchiectasis, emphysema, or even bronchiolitis with associated consolidation.[27-28] Once the diagnosis of ILD is made, the challenge of determining its aetiology arises, especially in the event of an acute clinical decline in lung function. If in diagnostic doubt, a video-assisted thoracoscopic surgery (VATS) biopsy should be considered to determine histology.[29]

In the case of methotrexate pneumonitis, a diffuse interstitial pattern on HRCT has been reported in more than 93% of patients; pleural thickening and, less commonly, pleural effusions are seen in a small number of patients.[17]

**Figure 3. Investigations involved in diagnosing RA-ILD (Adapted from Kelly et al[18] & Ooi et al[29])**




Although an open lung biopsy would help differentiate between RA-ILD and methotrexate pneumonitis, this is largely unnecessary. In general, methotrexate pneumonitis presents with an acute interstitial pneumonitis with cellular (lymphocytic) interstitial infiltrates with or without granulomas and, in severe cases, diffuse alveolar damage.[30] However, these patterns may coexist with RA-ILD HRCT findings, making it difficult to distinguish between the two. Moreover, the clinical presentation of RA-ILD and methotrexate-induced pulmonary toxicity are very similar. Hence, it is crucial to consult a radiologist who is experienced in ILD to make the distinction of RA-ILD from other causes of ILD that could render a similar HRCT pattern. In our patient, a diagnosis of stand-alone methotrexate pneumonitis seemed unlikely as she did not meet the above criteria and only presented after many years of methotrexate therapy.

Another factor that could complicate diagnosis is environmental or occupational exposures, which are often overlooked. It is stipulated that over 300 types of environmental triggers can increase the risk of developing hypersensitivity pneumonitis (extrinsic allergic alveolitis).[31] As such, a thorough clinical history should address possible inhaled allergens at home or in the workplace, including pet dander, mould, dust, and chemicals. Patients may present similarly to RA-ILD with dyspnoea, cough, malaise, and fever.[32] In long-term exposure, pulmonary fibrosis may also result.[32] Bilateral ground-glass opacities and/or centrilobar nodules often appear on HRCT, similar to that seen in RA-ILD.[33] However, the presence of lymphocytosis on bronchoalveolar lavage (BAL) and poorly formed non-caseating granulomas on transbronchial biopsy are more suggestive of hypersensitivity pneumonitis, somewhat differentiating this from RA-ILD.[31] Once a diagnosis of hypersensitivity pneumonitis is made, the avoidance of triggers and steroid therapy will improve symptoms. However, chronic damage may be irreversible. BAL would not differentiate between methotrexate pneumonitis and inhaled hypersensitivity pneumonitis.

The risk of developing pulmonary malignancy is increased in the presence of RA-ILD and immunosuppression.[34] Diffuse infiltrates may be present, indicating a haematogenous or, more likely, lymphangitic spread, which can be confirmed with BAL and transbronchial biopsy. Hence, in patients who do not respond to treatment, malignancy may be considered as an alternative diagnosis.[20]

In addition, RA patients receiving immunosuppressive therapy are more susceptible to lower respiratory tract infections, especially if they have an active lung disease, as seen in our case. Certain organisms such as *Mycobacterium avium, Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, and other fungal microbes have been identified to be responsible for causing such opportunistic infections and also cause a radiological appearance of ground-glass opacifications with interstitial infiltrates similar to that in RA-ILD.[20] In essence, all infective complications have to be investigated thoroughly and managed with the necessary cessation of immunosuppressive therapy and commencement of the relevant antibiotics according to the results of routine blood, urine, and BAL cultures.

*Management of RA-ILD*

According to the British Thoracic Society (BTS) guidelines published in 2008,[23] the

initial treatment of RA-ILD is typically with oral prednisolone at an initial dose of 0.5–1 mg/kg/day over a period of 1–3 months. This is then tapered down to a maintenance dose of 10 mg/day or 20 mg on alternate days and administered with immunosuppressants such as cyclophosphamide,[35] azathioprine,[36] penicillamine,[36] or methotrexate according to clinical response. Immunosuppressants have to be evaluated in line with response to steroids.

If the corticosteroids or immunosuppressants have failed, ciclosporin is effective as a steroid-sparing or adjuvant agent.[36-37] Cyclophosphamide has been found to be therapeutic in methotrexate-induced pneumonitis that has not been responsive to the usual methotrexate discontinuation, oxygen therapy, and/or corticosteroids.[38]

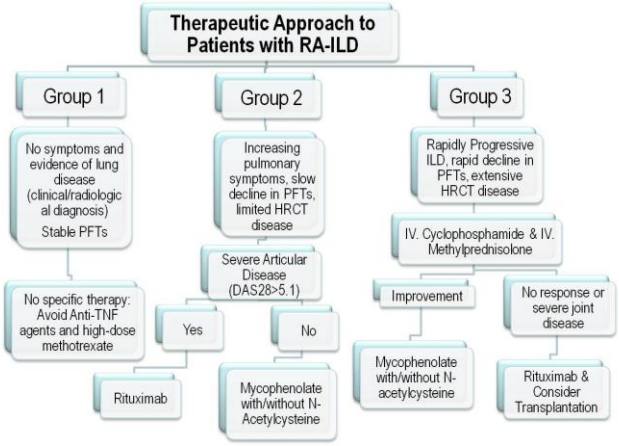
Due to the lack of controlled studies, optimal treatment of RA-ILD remains a matter of debate. A recent update on the management of RA-ILD suggests that patients can be broadly divided into 3 groups based on the extent of their disease, and this determines their treatment[40] (Figure 4), which is generally directed at disease control and treatment corresponding to histopathologic subtype. The first group comprises patients with asymptomatic ILD, whose pulmonary function and symptoms have to be monitored closely. If these are stable with no evidence of disease progression, then no specific therapy is indicated. The second group of patients includes those who are initially stable and asymptomatic but later experience progressive chest symptoms and a decline in lung function. Notably, most of these patients will still display limited disease signs on baseline HRCT. For this group, treating their pulmonary condition, in addition to a single or combined DMARD therapy for their joint disease, is the priority. If severe articular disease (disease activity score (DAS28) > 5.1) is evident, patients may benefit from biologic agents such as rituximab. In the absence of severe articular disease, the use of mycophenolate mofetil (1–2 g once daily) with or without acetylcysteine (600 mg three times daily) has been recommended.

The final group of patients are those with rapidly progressive or extensive RA-ILD involving more than 20% of the lungs. The first-line treatment is 6 cycles of intravenous cyclophosphamide 10–15 mg/kg in combination with methylprednisolone 7–10 mg/kg at 4–6-week intervals. Occasionally, mesna is prescribed to reduce the risk of haemorrhagic cystitis and later on, bladder cancer as a result of urothelial toxicity from cyclophosphamide therapy. Co-trimoxazole 960 mg three times daily may also be

prescribed as prophylaxis against pneumocystis pneumonia, and anticoagulation is commenced in patients with proven pulmonary embolism. Lung function has to be reassessed with repeat PFTs and HRCT post-treatment.

Most patients put on this treatment regimen have been found to exhibit clinical improvement and stability.[39] However, prognosis is poor in patients whose condition worsens further, and lung transplants may be considered in patients with advanced disease ($D_L$co < 40% predicted) or progressive (≥ 10% decline in FVC or ≥ 15% decline in FVC within 6 months of follow-up). Generally, patients over the age of 65 years and/or those with significant comorbidities are excluded from this criterion.[23,39]

**Figure 4. Algorithm of the proposed therapeutic approach to patients with RA-ILD (Adapted from White et al [28])**




Other ancillary treatments include annual influenza and pneumococcal vaccinations, which help prevent respiratory infections in RA-ILD patients, home oxygen support,[23] and smoking cessation with nicotine replacement therapy or buproprion.

Determining response to treatment is essential in monitoring therapeutic response and deciding how to manage patients further. Travis *et al.*[40] has defined this as a "10% improvement in the forced vital capacity (FVC) or 15% improvement in the $D_L$co at 12 weeks". Furthermore, HRCT is used to assess the response to treatment further by measuring the extent of lung involved. PFTs should be repeated annually and HRCT should only be done once every 2 years to minimize patients' exposure to radiation.

*Prognosis of RA-ILD*

RA-ILD is often associated with a poor prognosis, which largely depends on patients' age at the time of diagnosis and disease severity. Survival after diagnosis of RA-ILD has been estimated to be a median of approximately 3.5–5 years,[41] with a mean of 3 years,[27] and these figures have been relatively constant over the last 30 years. In addition, the type of ILD pattern illustrated on HRCT is an important determinant of prognosis and survival.[42] The majority of patients with RA-ILD have either UIP or NSIP.[21] UIP conveys the worst prognosis,[43,44] whereas patients with

NSIP carry a better prognosis and response to treatment, with the cellular subtype associated with higher survival rates as compared to the fibrotic subtype. COP (rarer) also displays a better prognosis and is more responsive to oral corticosteroid therapy.[4,5] Other indicators of poor prognosis include a low $D_L$CO (< 54%), desaturation (< 88%), extensive fibrosis, and extensive disease on HRCT.[21]

## Conclusion

The evidence available to guide management of RA-ILD remains limited. Our patient's ILD was difficult to manage due to uncertainties regarding its true aetiology, as there were similarities in clinical presentation. Moreover, radiological scans could not differentiate clearly between causes of ILD. Continuation on methotrexate could exacerbate our patient's lung disease but withdrawal of treatment could cause a relapse in her arthritis. At this point, there has been some clinical improvement in her symptoms on the tapering course of steroids and cessation of methotrexate therapy. However, her pulmonary damage is irreversible, suggesting it was RA-related ILD and not any other reversible causes, and her future management will thus involve multidisciplinary team input and is directed by her response to current treatment. This involves striking a balance between joint and pulmonary disease control, as well as rendering supportive care, with the aim of slowing down disease progression and managing her symptoms.

Newer medications such as mycophenolate mofetil, rituximab, and cyclophosphamide, and the emergence of newer biologic agents have provided a positive outlook for this disease. However, much research remains to be done in evaluating current treatment standards, developing new pharmacotherapy, and screening RA patients to detect pulmonary disease early.

**Learning Points**

***What is known already known***

- ILD is strongly associated with Rheumatoid Arthritis and its anti-rheumatic medications, such as methotrexate.
- ILD is usually treated with a tapering course of corticosteroids and/or immunosuppressants and managed holistically with ancillary treatments.

***What this study adds***

- The inclusion of a number of new agents (e.g. mycophenolate mofetil, rituximab, and cyclophosphamide) has provided a better outlook in treating ILD. Thorough consideration must be given to each individual patient's extent of disease, rate of progression and co-morbidities when deciding which treatments to administer.
- Prompt treatment delays disease progression of RA-ILD of arthritis and management revolves around symptom control.
- Multidisciplinary holistic care ensures best practice.

## References


1. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, *et al.* Interstitial lung disease in recent onset rheumatoid arthritis. *Am J Respir Crit Care Med.* 1997 Aug;156(2 pt 1):528-35. DOI: 10.1164/ajrccm.156.2.9609016.
2. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 2003 Aug;62(8):722-27. DOI: 10.1136/ard.62.8.722.
3. Young A, Koduri, Batley M, Kulinskaya E, Gough A, Norton S, *et al.* Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford).* 2007 Feb;46(2):350-7. DOI: 10.1093/rheumatology/kel253.
4. McDonagh J, Greaves M, Wright AR, Heycock C, Owen JP, Kelly C. High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease. *Br J Rheumatol.* 1994 Feb;33(2):118-22. DOI: 10.1093/rheumatology/33.2.118.
5. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, *et al.* Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med.* 2008 Jan 28;168(2);159-66. DOI: 10.1001/archinternmed.2007.59.
6. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, Kloppenburg M, de Vries RR, le Cessie S, *et al.* Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Ann Rheum Dis.* 2006 Mar;65(3):366-71. DOI: 10.1136/ard.2005.041079.
7. Weyand CM, Schimdt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. *Arthritis Rheum.* 1998 May;41(5),817-22. DOI: 10.1002/1529-0131(199805)41:5<817::AID-ART7>3.0.CO;2-S.
8. Turesson C, Jacobsson LTH. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol.* 2004;33(2):65-72. DOI: 10.1080/03009740310004621.
9. Sugiyama Y, Ohmo S, Kano S, Maeda H, Kitamura S. Diffuse panbronchiolitis and rheumatoid arthritis: a possible correlation with HLA-B54. *Intern Med.* 1994;33(10):612-4. DOI: 10.2169/internalmedicine.33.612.
10. Charles PJ, Sweatman MC, Marckwick JR, Maini RN. HLA-B40: a marker for susceptibility to lung disease in rheumatoid arthritis. *Dis Markers.* 1991 Mar-Apr;9(2):97-101.
11. Alexiou I, Germenis A, Koutroumpas A, Kontogianni A, Theodoriou K, Sakkas LI. Anti-cyclic citrullinated peptide-2 (CCP2) autoantibodies and extra-articular manifestations in Greek patients with rheumatoid arthritis. *Clin Rheumatol.* 2008 Apr;27(4):511-3. DOI: 10.1007/s10067-007-0800-1.
12. Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol.* 2008 May;20(3):340-6. DOI: 10.1097/BOR.0b013e3282f798ed.
13. Inui N, Enomoto N, Suda T, Kageyama Y, Watanabe H, Chida K. Anti-cyclic citrullinated peptide antibodies in lung diseases associated with rheumatoid arthritis. *Clin Biochem.* 2008 Sep;41(13):1074-7. DOI: 10.1016/j.clinbiochem.2008.06.014.
14. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L. Methotrexate, rheumatoid arthritis and infection risk—what is the evidence? *Rheumatology (Oxford).* 2009 Aug;48(8):867-71. DOI: 10.1093/rheumatology/kep101.
15. Jakubovic BD, Donovan A, Webster PM, Shear NH. Methotrexate-induced pulmonary toxicity. *Can Respir J.* 2013 May-Jun;20(3):153-5.
16. Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology (Oxford).* 2004 Feb;43(2):143-7. DOI: 10.1093/rheumatology/keg466.
17. Kremer JM, Alarcón GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, *et al.* Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum.* 1997 Oct;40(10):1829-37. DOI: 10.1002/art.1780401016.
18. Kelly C, Saravanan V. Treatment strategies for a rheumatoid arthritis patient with interstitial lung disease. *Expert Opin Pharmacother.* 2008 Dec;9(18):3221-30. DOI: 10.1517/14656560802591430.
19. Gaffo AL, Alarcón GS. Methotrexate is not associated with progression of interstitial lung disease in rheumatoid arthritis. *Arch Intern Med.* 2008 Sep 22;168(17):1927-8. DOI: 10.1001/archinte.168.17.1927.

20. Hamblin MJ, Horton MR. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. *Pulm Med.* 2011;2011:872120. DOI: 10.1155/2011/872120.

21. Lake F, Proudman S, Rheumatoid arthritis and lung disease: from mechanism to a practical approach. *Semin Respir Crit Care Med.* 2014 Apr;35(2):222-38. DOI: 10.1055/s-0034-1371542.

22. Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. *J Rheumatol.* 1987 Dec;14(6):1164-71.

23. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, *et al.* Interstitial lung disease guideline: The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax.* 2008;63 Suppl 5:v1-58. DOI: 10.1136/thx.2008.101691.

24. Sathi N, Urwin T, Desmond S, Dawson JK. Patients with limited rheumatoid arthritis-related interstitial lung disease have a better prognosis than those with extensive disease. *Rheumatology.* 2011 Mar;50(3) 620. DOI:10.1093/rheumatology/keq426.

25. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med.* 2008 Jun 1;177(11):1248-54. DOI: 10.1164/rccm.200706-877OC.

26. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, *et al.* Rheumatoid arthritis-related lung diseases: CT findings. *Radiology.* 2004 Jul;232(1):81-91. DOI: 10.1148/radiol.2321030174.

27. Akira M, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis associated lung disease: CT patterns and their courses. *J Comput Assist Tomogr.* 1999 Nov-Dec;23(6):941-8. DOI: 10.1097/00004728-199911000-00021.

28. White ES, Tazelaar HD, Lynch JP 3rd. Bronchiolar complications of connective tissue diseases. *Semin Respir Crit Care Med.* 2003 Oct;24(5):543-66. DOI: 10.1055/s-2004-815603.

29. Ooi A, Ivenger S, Ferguson J, Ritchie AJ. VATS lung biopsy in suspected, diffuse interstitial lung disease provides, and alters management strategies. *Heart Lung Circ.* 2005 Jun;14(2):90-2. DOI: 10.1016/j.hlc.2005.01.002

30. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J.* 2000 Feb;15(2):373-81. DOI: 10.1034/j.1399-3003.2000.15b25.x

31. Selman M. Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clin Chest Med.* 2004 Sep;25(3):531-47. DOI:10.1016/j.ccm.2004.04.001.

32. Yi ES. Hypersensitivity pneumonitis. *Crit Rev Clin Lab Sci.* 2002 Nov;39(6):581-629. DOI: 10.1080/10408360290795583.

33. Glazer CS, Rose CS, Lynch DA. Clinical and radiologic manifestations of hypersensitivity pneumonitis. *J Thorac Imaging.* 2002 Oct;17(4):261-72. DOI: 10.1097/00005382-200210000-00003.

34. Rajasekaran A, Shovlin D, Saravanan V, Lord P, Kelly C. Interstitial lung disease in patients with rheumatoid arthritis: comparison with cryptogenic fibrosing alveolitis over 5 years. *J Rheumatol.* 2006 Jul;33(7):1250-3.

35. Nanki N, Fujita J, Yamaji Y, Maeda H, Kurose T, Kaji M, *et al.* Nonspecific interstitial pneumonia/fibrosis completely recovered by adding cyclophosphamide to corticosteroids. *Intern Med.* 2002 Oct;41(10):867-70. DOI: 10.2169/internalmedicine.41.867.

36. Chang HK, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. *J Korean Med Sci.* 2002 Apr;17(2):270-3. DOI: 10.3346/jkms.2002.17.2.270.

37. Puttick MP, Klinkhoff AV, Chalmers A, Ostrow DN. Treatment of progressive rheumatoid interstitial lung disease with cyclosporine. *J Rheumatol.* 1995 Nov;22(11):2163-5.

38. Suwa A, Hirakata M, Satoh S, Mimori T, Utsumi K, Inada S. Rheumatoid arthritis associated with methotrexate-induced pneumonitis: improvement with i.v. cyclophosphamide therapy. *Clin Exp Rheumatol.* 1999 May-Jun;17(3):355-8.

39. Malik S, Saravanan V, Kelly C. Interstitial lung disease in rheumatoid arthritis: an update on diagnosis and management. *Int J Clin Rheumatol.* 2012 Aug 6;7(3):297-308. DOI: 10.2217/IJR.12.24.

40. Travis WD, Hunninghake G, King TE Jr, Lynch DA, Colby TV, Galvin JR, *et al.* Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. *Am J Respir Crit Care Med.* 2008 Jun 15; 77(12):1338-47.

DOI: 10.1164/rccm.200611-1685OC.

41. Hakala M. Poor prognoses in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis. *Chest.* 1988;93(1):114-8. DOI: 10.1378/chest.93.1.114.
42. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. *Chest.* 2009 Nov;136(5):1397-405. DOI: 10.1378/chest.09-0444.
43. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, *et al.* Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest.* 2005 Jun;127(6):2019-27. DOI: 10.1378/chest.127.6.2019.
44. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, *et al.* Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J.* 2010 Jun;35(6):1322-8. DOI: 10.1183/09031936.00092309.
45. Yoo JW, Song JW, Jang SJ, Lee CK, Kim MY, Lee HK, *et al.* Comparison between cryptogenic organizing pneumonia and connective tissue disease-related organizing pneumonia. *Rheumatology (Oxford).* 2011 May;50(5):932-8. DOI: 10.1093/rheumatology/keq410.