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SHORT REPORT

Management of interstitial lung disease in patients with autoimmune disease-related interstitial lung disease

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ABSTRACT

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases. A proportion of patients with autoimmune disease associated-ILDs develop progressive pulmonary fibrosis. Regular monitoring of patients with pulmonary fibrosis is recommended to enable prompt detection of progression and initiation or escalation of therapy if needed. However, there is no established algorithm for the treatment of autoimmune disease associated-ILDs. In this article, we present three case studies that demonstrate the challenges in the diagnosis and management of patients with autoimmune disease associated-ILDs and the importance of taking a multidisciplinary approach to their care.

Key words: rheumatoid arthritis; dermatomyositis; polymyositis; pulmonary fibrosis; systemic scleroderma.

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Introduction

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases including rheumatoid arthritis (RA) [1], systemic sclerosis (SSc) [2] and polymyositis/dermatomyositis [3]. The course of ILD is variable. Some patients with fibrosing autoimmune diseases associated-ILD develop a progressive fibrosing phenotype characterized by increasing fibrosis on high-resolution computed tomography (HRCT), decline in lung function, and early mortality [2-4]. Immunosuppression is the standard of care to treat autoimmune diseases and has been shown to slow the progression of SSc-ILD [5-7]. Recently the interleukin-6 (IL-6) receptor antagonist tocilizumab was approved by the FDA for slowing the rate of decline in lung function in patients with SSc-ILD. There are limited data on the efficacy of immunosuppressants in patients with autoimmune disease-related ILDs other than SSc-ILD [8-17]. Recently, rituximab was shown to be effective in improving lung function in patients with autoimmune disease-related ILD including SSc, idiopathic inflammatory myositis (including polymyositis or dermatomyositis), or mixed connective tissue disease (CTD) with associated severe or progressive ILD, with fewer adverse events compared to cyclophosphamide [17]. Based on data from randomized placebo-controlled trials showing that it slows decline in lung function in patients with SSc-ILD [18], idiopathic pulmonary fibrosis (IPF) [19] and progressive fibrosing ILDs other than IPF [20], nintedanib has been approved by the FDA and other regulators for the treatment of these ILDs. Data on the benefits of combination therapy for autoimmune disease-related-ILD remain sparse, and there is no established algorithm for the initiation or escalation of pharmacotherapy in these patients. In this article, we discuss three case studies that illustrate the challenges in the diagnosis, monitoring and management of autoimmune disease associated-ILDs.

A case of progressive RA-ILD

A 62-year-old male with coronary artery disease treated with stent placement ten years prior was evaluated in the pulmonary

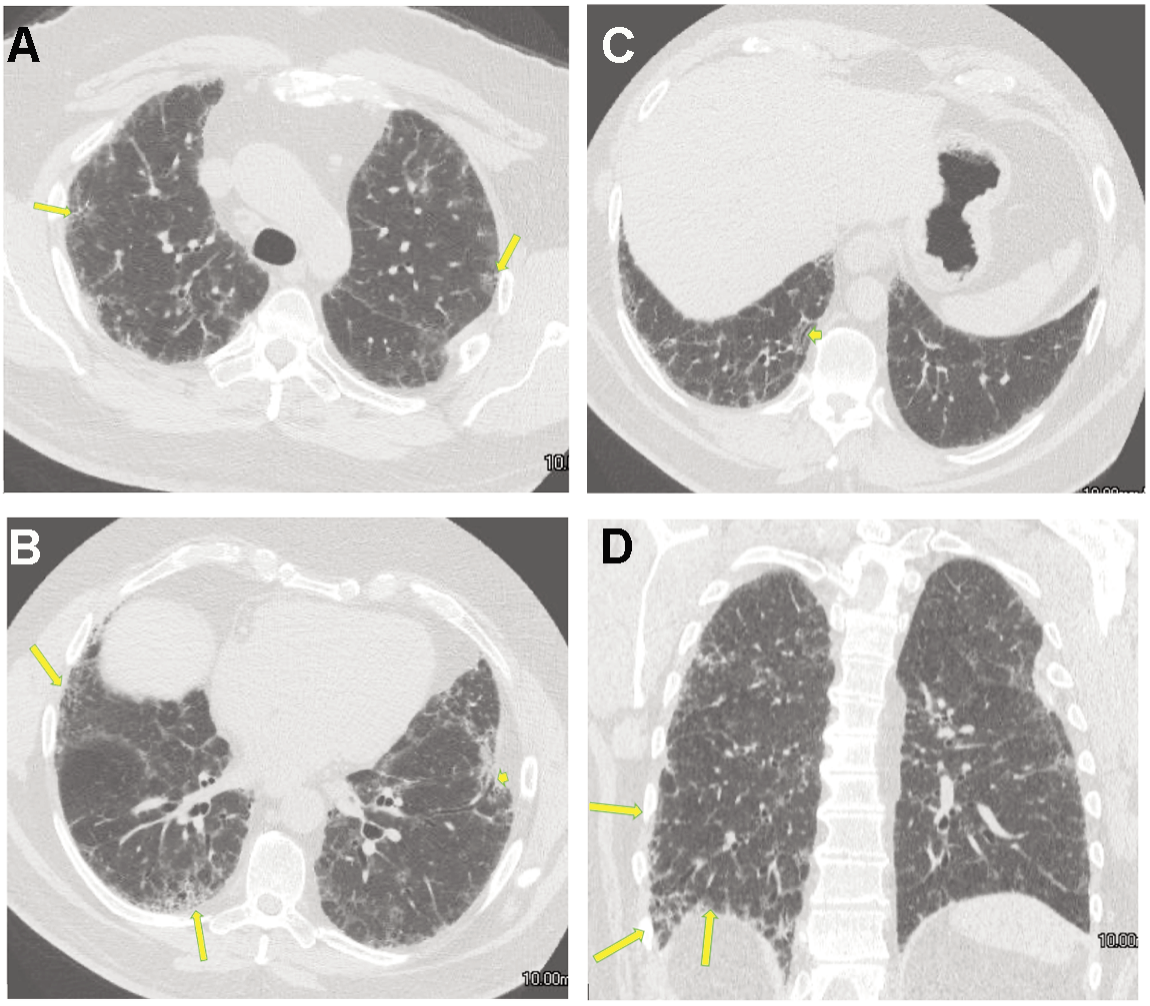

Figure 1. HRCT scans at presentation from a patient with RA-ILD. Axial image at the level of the aortic arch (A), axial image at right inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal HRCT image (D) illustrating the craniocaudal disease distribution. Areas of peripheral reticulation (arrows in A and B) are more severe in the bases. Note areas of traction bronchiectasis/bronchiolectasis (arrowheads in C). No definitive honeycombing is seen and the apparent ground glass densities are limited to areas of reticulation, likely reflecting microscopic fibrosis. The right basilar reticulation extending up the lateral sidewall (arrows in D) is common in a UIP pattern of lung injury. This is a probable UIP pattern given the lack of features inconsistent with UIP.

clinic after presenting to his primary care physician with dyspnea on exertion. He was unable to walk more than 500 meters without feeling out of breath. He also complained of a dry cough throughout the day without aggravating or relieving factors. A review of symptoms revealed joint pain, especially in the hands, associated with morning stiffness, and gastroesophageal reflux disease (GERD). He was a former smoker (30 pack/years) who had quit smoking a few months prior to his clinic visit. He had worked as a machinist for 32 years and been exposed to fine metal particles but had no other environmental exposures. His medications included aspirin, atorvastatin and ezetimibe. His physical examination was significant for bilateral basal crackles on respiratory exam and swelling in his bilateral metacarpophalangeal (MCP) joints.

Serological studies were notable for an increased rheumatoid factor level (354 IU/mL) and IgG anti-cyclic citrullinated peptide (anti-CCP) antibody level of >150 units. Pulmonary function tests (PFTs) showed a forced vital capacity (FVC) of 2.5 L (50% predicted), forced expiratory volume in one second (FEV_1) of 2.10 L (60% predicted), FEV_1/FVC ratio of 70% (84% predicted), total lung capacity (TLC) of 3.56 L (48% predicted), residual volume (RV) of 1.06 L (41% predicted), and diffusion capacity of the lung for carbon monoxide (DLco) of 14 mL/mmHg/min (48% predicted). Supplemental oxygen was required on six-minute walk testing with a nadir oxygen saturation of 91%. Cardiac echocardiography showed a left ventricular ejection fraction (LVEF) of >55%, normal right ventricular systolic function and borderline mitral valve prolapse. Chest roentgenography (X-ray) demonstrated diffuse reticulations. HRCT demonstrated a probable usual interstitial pneumonia (UIP) pattern (Figures 1 and 2). A barium esophagram was negative for laryngeal penetration or tracheal aspiration.

The patient was referred to a rheumatologist who confirmed a diagnosis of RA. After multidisciplinary discussion (MDD) including review of the clinical features, imaging and serologies, a diagnosis was made of RA-associated ILD (RA-ILD). Treatment options were discussed with the patient, and he was started on mycophenolate mofetil, in addition to pantoprazole for GERD. The patient developed fatigue and nausea soon after starting mycophenolate mofetil and so, after confirming thiopurine methyl transferase activity levels were normal, he was switched to azathioprine. He was unable to tolerate azathioprine due to nausea. Meanwhile, the patient developed increased joint pain in his bilateral MCP joints. His chest imaging was predominantly fibrotic and did not reveal ground glass opacities. After MDD between pulmonologists and rheumatologists, a decision was made to treat his joint pain with hydroxychloroquine 400 mg daily and oral methotrexate 15 mg weekly with daily folic acid. Close follow up on a quarterly basis was planned, including PFTs. The patient underwent annual six-minute walk testing and echocardiography to screen for pulmonary hypertension. Over the next two years, his joint symptoms were well controlled, with stable PFTs and no changes in echocardiogram.

Two years after his first visit, the patient had worsening dyspnea on exertion. His spirometry revealed an FVC of 1.74 L (41% predicted), FEV_1 of 1.74 L (45% predicted) and DLco of 9 mL/mmHg/min (32% predicted). On six-minute walk testing, he required 4 L of oxygen. HRCT at this time demonstrated progressive fibrosis with a typical UIP pattern with clear honeycombing (Figure 3). His echocardiogram was similar to baseline. He was admitted to hospital and underwent a left heart catheterization, which revealed mild non-obstructive coronary artery disease. Right heart catheterization was not consistent with pulmonary hypertension. Given the progression of ILD and persistent extrapulmonary symptoms, the decision was made in an MDD to discontinue methotrexate and initiate rituximab. Three months after his first rituximab infusion, he was admitted to the hospital with fever. Laboratory tests were significant for a white count of 1970 cells per mL of blood with an absolute neutrophil count of 0. Work-up revealed chest wall cellulitis, for which he was treated with broad spectrum antibiotics. After consultation with the hematology team, it was deemed that his neutropenia was secondary to rituximab therapy. He was discharged from hospital after his white count had recovered to 3740 cells per mL with a ten-day course of amoxicillin-clavulanate. During follow up in the pulmonary clinic two weeks after discharge, spirometry was notable for an FVC of 1.88 L (36% predicted), FEV_1 of 1.58 L (41% predicted) and DLco of 11.8 mL/mmHg/min (41% predicted). Due to worsening FVC and respiratory symptoms, nintedanib was initiated for progressive fibrosing ILD and the patient was evaluated by the lung transplant team.

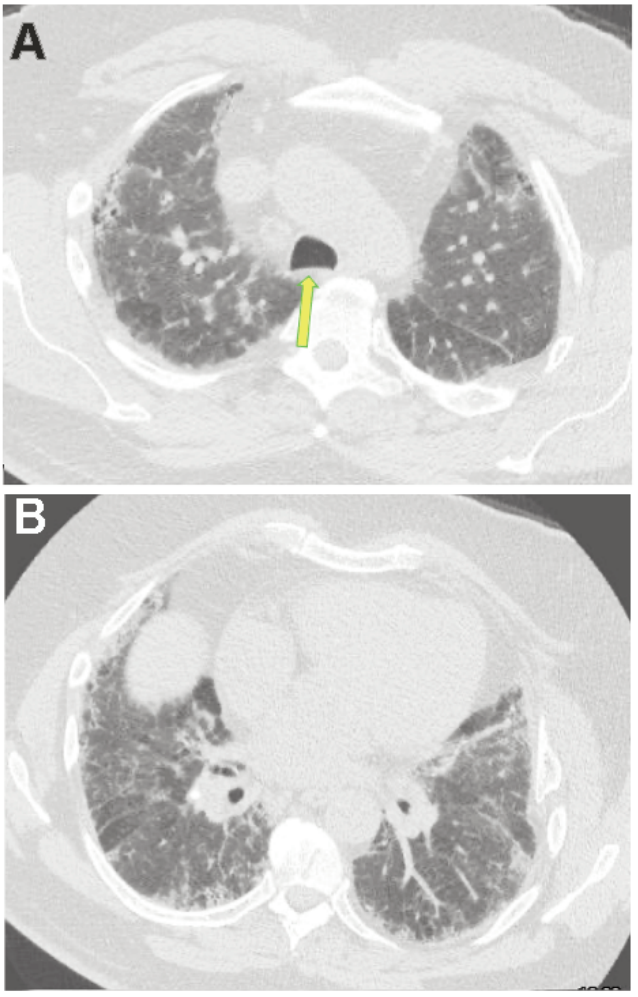

Figure 2. Expiratory HRCT images at presentation from a patient with RA-ILD at the level of the aortic arch (A) and left inferior pulmonary vein ostium (B). Images demonstrate a normal homogenous increase in lung attenuation with expiration and no significant air trapping. Significant air trapping (diffuse in three or more lobes) would suggest an alternative diagnosis such as fibrotic hypersensitivity pneumonitis. Note the flattening of the membranous trachea (arrow) suggesting adequate expiratory effort. If the trachea maintains a rounded configuration on both the inspiratory and expiratory scans, this suggests the expiratory effort was poor, which limits the ability to assess for air trapping.

Three months later, his oxygen requirement had increased to 5 L on exertion with no change in his echocardiogram. HRCT at this time demonstrated no appreciable change, with no imaging manifestations of a superimposed infection or an acute exacerbation. After discussion with the rheumatology team, a plan was made to initiate intravenous cyclophosphamide, but in the interim, the patient was listed for a lung transplant. He received a single lung transplant and was doing well 9 months later.

A case of SSc-ILD

A 50-year-old woman presented at our tertiary referral center for evaluation of ILD. She had no medical history other than back and knee surgeries until a few months prior, when she noticed skin tightening on her hands and subsequent joint pain. She had no family history of pulmonary disease or autoimmune conditions. She had never smoked and had no occupational or environmental exposures. She was positive for Scl-70 and had occasional Raynaud's phenomenon, GERD, sicca, and telangiectasias. She was diagnosed with SSc by her rheumatologist. After a chest X-ray, she was told that there might be some scarring in her lungs. She was started on oral prednisone 20 mg daily and transitioned to mycophenolate 1 g twice daily. She was started on esomeprazole 40 mg daily to treat symptoms of acid reflux. By the next month, she noted worsening dyspnea, which progressed to limiting her daily activities, as well as a non-productive cough which prompted referral to our ILD center. No fevers, chills, chest pain, or pedal edema were noted.

On initial exam at our center, she had an oxygen saturation of 97% at rest. She had bilateral lower lung field dry crackles on exam, and sclerodactyly in both hands. No fingertip ulcerations were noted. Her initial pulmonary function tests revealed FVC of 2.28 L (56% predicted), FEV_1 of 1.98 L (62% predicted), FEV_1/FVC ratio of 87%, TLC of 3.49 L (62% predicted) and DLco of 6.6 mL/mmHg/min (27% predicted). She did not require oxygen during a six-minute walk test. Her serologies were confirmed positive for Scl-70 and anti-nuclear antibody. HRCT demonstrated a non-specific interstitial pneumonia (NSIP) pattern of lung injury (Figures 4 and 5). With this clinical presentation, a diagnosis of SSc-ILD was confirmed by MDD. Mycophenolate was titrated to 1.5 g twice daily. Her laboratory measurements, including white blood cell count, were monitored quarterly.

An echocardiogram showed LVEF >55%, right ventricular systolic pressure 30-40 mmHg and normal right ventricular systolic function. She underwent right heart catheterization, which showed mean pulmonary artery pressure of 25 mmHg (38,13 mmHg) with normal pulmonary capillary wedge pressure. She experienced progressive worsening of dyspnea and cough. Her skin symptoms remained stable. PFTs 6 months later showed an FVC of 2.20 L (54% predicted), FEV_1 of 1.96 L (61% predicted), FEV_1/FVC ratio of 89%, and DLco of 9.5 mL/mmHg/min (39% predicted). Her HRCT showed an increase in fibrotic changes (Figure 6). She was started on nintedanib 150 mg twice daily, in addition to the mycophenolate mofetil. Six months later, she continued to have exercise limitations but her PFTs had stabilized. PFTs showed an FVC of 2.16 L (53% predicted), FEV_1 of 1.96 L (62% predicted), FEV_1/FVC ratio of 89%, and DLco of 8.5 mL/mmHg/min (35% predicted).

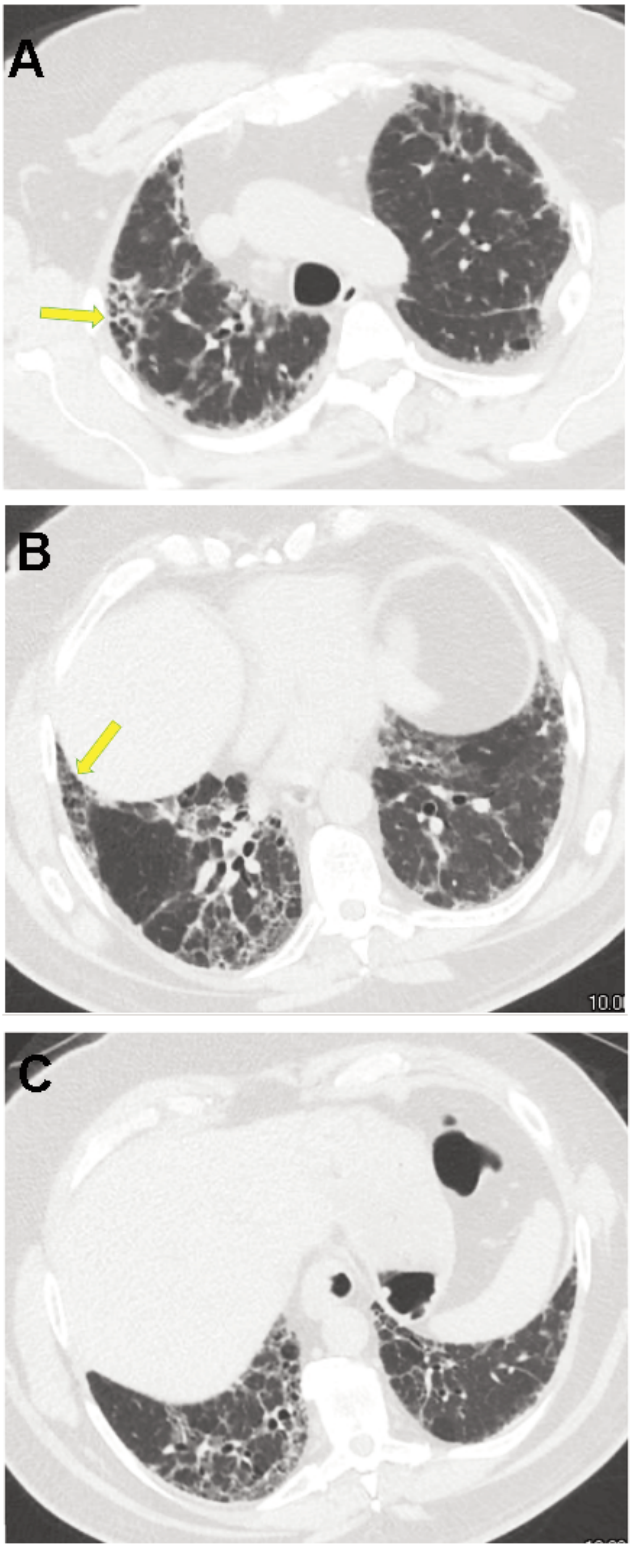

Figure 3. Axial HRCT scans at follow up from a patient with RA-ILD at the level of the aortic arch (A), right inferior pulmonary vein ostium (B), and just above the hemidiaphragms (C). The fibrosis has clearly progressed with worsening of the peripheral reticulation and traction bronchiectasis/bronchioloectasis. Honeycombing (arrows) is present. This is a UIP pattern of lung injury.

A case of anti-synthetase syndrome with myositis and ILD

A 58-year-old woman presented to our tertiary referral center with recurrent pneumonia. She denied any respiratory symptoms until six months prior to presentation when she developed pneumonia. She was treated with antibiotics and steroids and her symptoms improved until steroids were discontinued, at which time she developed recurrent cough and dyspnea. PFTs showed an FVC of 1.2 L (33% predicted), FEV_1 of 1.01 L (36% predicted) and FEV_1/FVC ratio of 84%. She was hospitalized several times (outside our center) and intubated for nine days three months after her first presentation for respiratory failure, which was thought to be secondary to pneumonia. COVID-19 testing was negative and bronchoalveolar lavage was negative for malignancy and infection. A transbronchial biopsy was not performed. The chest CT from the outside facility at the time of the respiratory failure showed multifocal ground glass and consolidative opacities that were reported as concerning for multifocal infection (Figure 7). An echocardiogram showed a normal LVEF and a right ventricular systolic pressure of 34 mmHg. She was a lifelong non-smoker and had no mold or feather exposures, but she lived on a pasture on which hay is baled, in a town with an abundance of cotton and peanut farms. Her family history is unknown, as she was adopted. She had neuropathy of unknown etiology that started a few years prior.

Laboratory tests outside our center showed a creatine kinase of 4079 U/L, aldolase of 41 U/L, a positive anti-Jo-1 antibody and positive anti-Ro 52kD at 130. Based on these data, the patient was diagnosed with anti-synthetase syndrome with myositis and ILD. Prednisone, which she had been on after her most recent hospitalization, was increased from 40 mg daily to 60 mg daily and mycophenolate mofetil was initiated at 500 mg twice daily. She

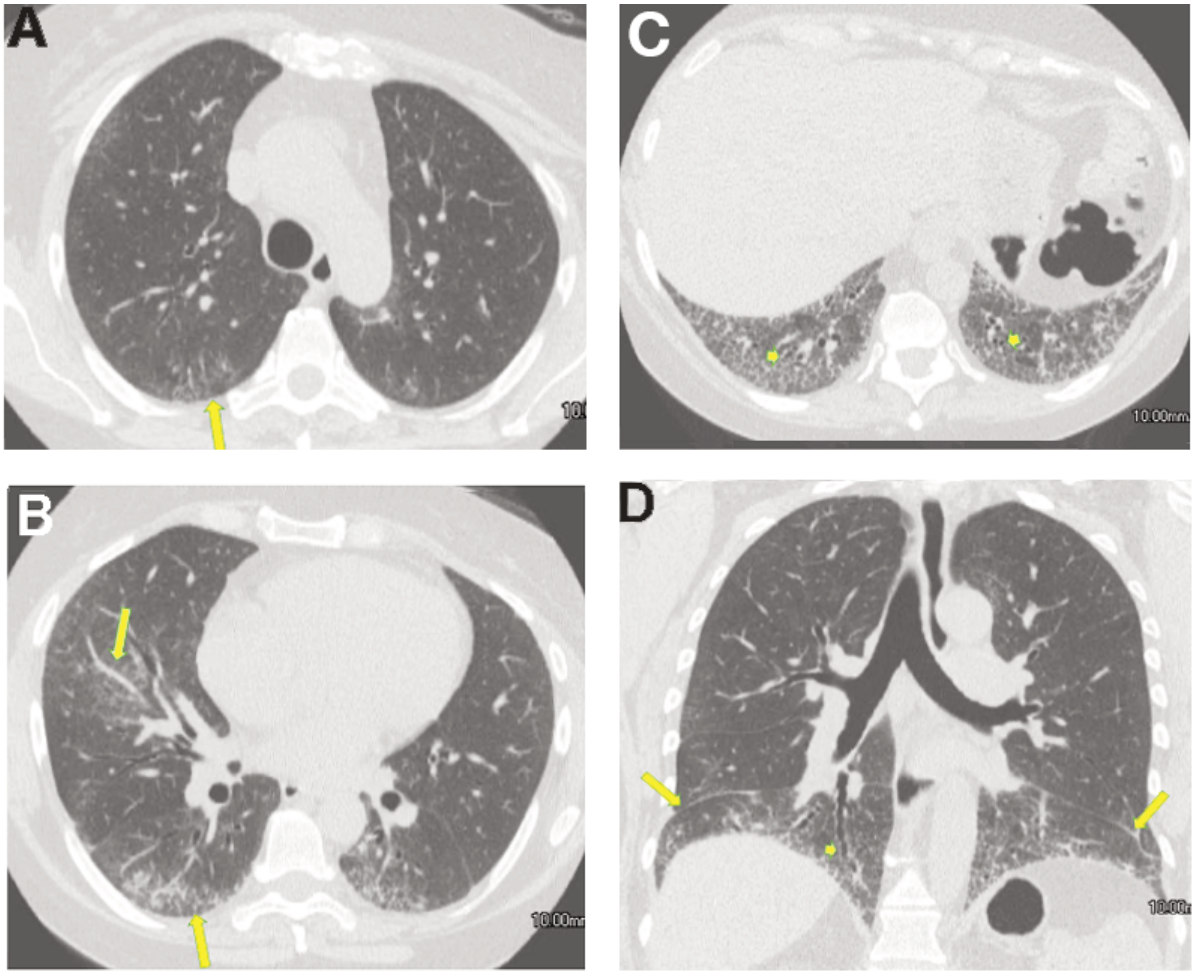

Figure 4. HRCT images at presentation in a patient with SSc-ILD. Axial image at the level of the aortic arch (A), axial image at the left inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal image (D) demonstrating the craniocaudal distribution of disease. Note the ground glass densities (arrows in A and B) with mild involvement of the upper lobes but progressively more severe involvement towards the bases. Extensive reticulation is seen in the bases with mild traction bronchiectasis/bronchioloectasis (arrowheads in C). Sparing of the immediate subpleural lung is best seen posteriorly on the right in B. Basilar predominant ground glass densities with traction bronchiectasis and subpleural sparing is typical of an NSIP pattern of lung injury. In the coronal HRCT image, unlike a UIP pattern of lung injury, NSIP shows a more homogenous basilar predominance and does not extend up the lateral sidewall. Note the volume loss characterized by the downward fissural displacement (arrows in D) as well as the traction bronchiectasis (arrowhead in D).

was started on trimethoprim/sulfamethoxazole for pneumocystis jiroveci pneumonia (PJP) prophylaxis.

Since her prolonged hospitalization with intubation, she maintained a supplemental oxygen requirement (2-3 L/min) and experienced muscle weakness. She reported low grade fevers, dry mouth, hair loss and parasthesia but denied weight loss, night sweats, dry eyes, nasal or oral ulcers, or Raynaud's phenomenon. She reported occasional sinus drainage with associated cough. Dyspnea on exertion remained stable with no chest pain. She reported gastroesophageal reflux and occasional dysphagia to pills and some foods. She noted redness over the MCP joints and cuticles of the fingers and joint pain and swelling, which worsened when off prednisone.

On evaluation at our center, her physical examination was notable for dry mouth. Her heart rate was tachycardic but with regular rhythm. Lung examination was notable for crackles at the bases bilaterally. Musculoskeletal examination showed no swelling or tenderness of the joints. Neurologic examination was notable for a hip flexor strength of 4-/5 and ability to stand on her own from a chair, which she noted was an improvement from the previous week, and upper extremity strength of 4+/5. Skin examination was pertinent for erythema of the cuticles bilaterally and at the distal tips of the fingernails.

In a multidisciplinary approach between pulmonary and rheumatology, mycophenolate mofetil was increased to 1000 mg twice daily and her respiratory status was reassessed. Creatine kinase level improved from 971 to 338 U/L. Prednisone was reduced from 60 mg daily to 50 mg daily, but the patient had worsening respiratory symptoms and worsening muscle weakness and tenderness, so the dose was increased back to 60 mg daily. As no notable improvement in respiratory status was observed with high doses of steroids plus mycophenolate mofetil over approximately six weeks and prednisone could not be tapered, alternative treatment options were explored. It was decided to add rituximab and increase the mycophenolate mofetil dose to 1500 mg twice daily until the rituximab infusion was initiated. The patient underwent infusion of rituximab-pvvr (a biosimilar to rituximab) (1000 mg x 2 doses, 2 weeks apart) and mycophenolate mofetil was decreased to 1000 mg twice daily, with a plan to decrease to 500 mg twice daily. The patient was able to decrease the prednisone dose to 40 mg daily and then to 25 mg daily three months after the rituximab-pvvr infusion. She was also started on alendronate for prevention of glucocorticoid-induced osteoporosis. Three months after rituximab-pvvr infusion, the patient's oxygen requirement had reduced to 2 L/min, mainly on exertion, with no flares, improvement in muscle pain, and 5/5 muscle strength on physical examination. The patient developed varicella zoster infection two and a half months after rituximab-pvvr infusion and was treated with anti-viral therapy. One year after presentation to our center, the patient was able to wean off oxygen and had 5/5 muscle strength in the upper and lower extremities. Her muscle enzymes normalized. She continues anti-CD20 therapy every six months and has been able to taper off mycophenolate mofetil and corticosteroids.

Discussion and Conclusion

ILD is a common manifestation of autoimmune diseases but its diagnosis in clinical practice is often delayed due to multiple factors. While PFTs can be utilized as a screening tool in some instances, diagnosis of ILD requires HRCT with inspiratory and expiratory views. All three of our ILD cases were diagnosed based on a compilation of clinical presentation, exposure history, physical exam, serologies and HRCT findings following MDD. Multiple studies have shown the utility of MDD to improve diagnostic accuracy for ILD and MDD has been endorsed in international consensus guidelines for the diagnosis of ILD [21]. In some cases, evaluation of an HRCT scan, laboratory data and clinical features do not enable a definite diagnosis of ILD to be made. Dynamic discussion among pulmonologists, radiologists, pathologists and rheumatologists is important to decide whether bronchoalveolar lavage or surgical lung biopsy is warranted to provide additional information [21-23]. The potential benefit of a surgical lung biopsy in confirming a diagnosis should be weighed against the risk of mortality due to the procedure [24-26]. Transbronchial lung cryobiopsy may be preferred to surgical lung biopsy at centers with the appropriate expertise [21].

In this report, the cases with RA-ILD and anti-synthetase syndrome with myositis and ILD had CT scans showing evidence of ILD before their diagnosis of autoimmune disease was confirmed. This demonstrates that, just as it is important that patients with autoimmune diseases are evaluated for ILD, patients with ILD should be evaluated for autoimmune disease. A study of 114 patients referred to an ILD clinic found that 15% of patients were diagnosed with a CTD following evaluation for ILD [27]. A recent analysis of US insurance claims data found that about 5% of patients with SSc had claims for ILD >1 year prior to a claim for SSc [28].

Decisions on how to treat ILDs other than IPF can be challenging and ideally should be based on MDD [26,29]. Patients with autoimmune disease-related ILDs often respond well to immunosuppressants, at least initially. The practice for management of the different autoimmune disease-related ILDs varies across centers, with clinical decisions influenced mainly by the findings of Scleroderma Lung Studies I and II, conducted in patients with SSc-ILD [5,6]. However, some patients, such as our patient with anti-synthetase syndrome, do not respond to mycophenolate mofetil or azathioprine and require escalation to rituximab or cyclophosphamide. While previous practices were based on small retrospective studies and clinical experience, recently published data from the RECITAL and DESIRES trials now support the use of these medications in patients with autoimmune disease-related ILDs [17,30]. Among patients with progressive autoimmune disease-related ILD, rituximab and cyclophosphamide were effective in

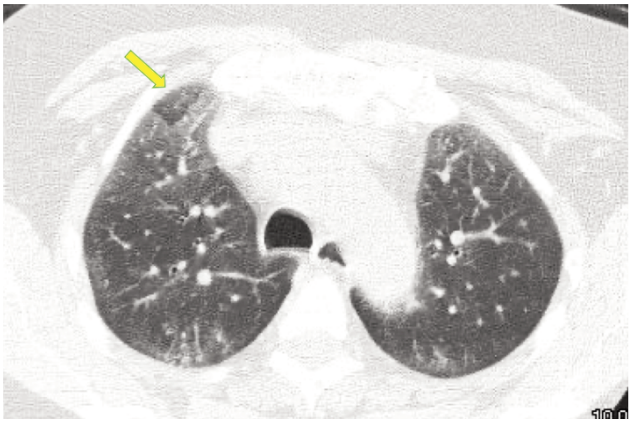

Figure 5. Prone expiratory HRCT image at presentation in a patient with SSc-ILD. Image demonstrates no significant air trapping (diffuse and bilateral involving three or more lobes). Mild lobular air trapping (arrow) is seen in the anterior right upper lobe. This patient was imaged in the prone position and the anterior lungs are dependent. Isolated lobular air trapping in dependent portions of the lung is common and should be considered physiologic and not indicative of significant small airways disease.

improving lung function; rituximab is better tolerated in this patient population [17]. We decided to use an approach that has not been described in the literature and switched to rituximab-pvvr, a biosimilar. This enabled a reduction in corticosteroid dose and led to a reduction in creatine kinase, consistent with previous studies [9,11]. Our patient was anti-Ro-52kD-positive, an autoantibody profile that has been shown to respond better to rituximab than to other immunosuppressants [31]. One of the main complications of combination immunosuppression and anti-CD20 therapy is infection, including PJP [11,31]. Our patient was given trimethoprim/sulfamethoxazole for PJP prophylaxis, but nonetheless developed varicella zoster infection. Clinicians should be mindful of PJP prophylaxis and administration of vaccines, including those for influenza and COVID-19, before initiation of anti-CD20 therapy and immunosuppression.

Unfortunately, some patients with progressive ILD continue to progress despite treatment. Guidelines recently published by an international group of pulmonology societies provided criteria for progressive pulmonary fibrosis in patients with ILDs other than IPF, based on worsening of symptoms, radiological findings, and lung function [21]. As demonstrated by all our cases, regular follow up of patients with fibrosing ILDs is important to enable prompt detection of progression of ILD or worsening of other manifestations of autoimmune disease or comorbidities so that changes to therapy can be implemented in a timely manner [26,32]. Equally important is an understanding of the risk factors for ILD progression in this patient population and having a proactive approach. Older age, male sex, and lower lung function are associated with a more progressive phenotype [33,34]. Patients with RA-ILD who have a UIP pattern on HRCT have been shown to have a worse prognosis than patients with a an NSIP pattern [35,36].

The INBUILD trial enrolled patients with fibrosing ILDs other

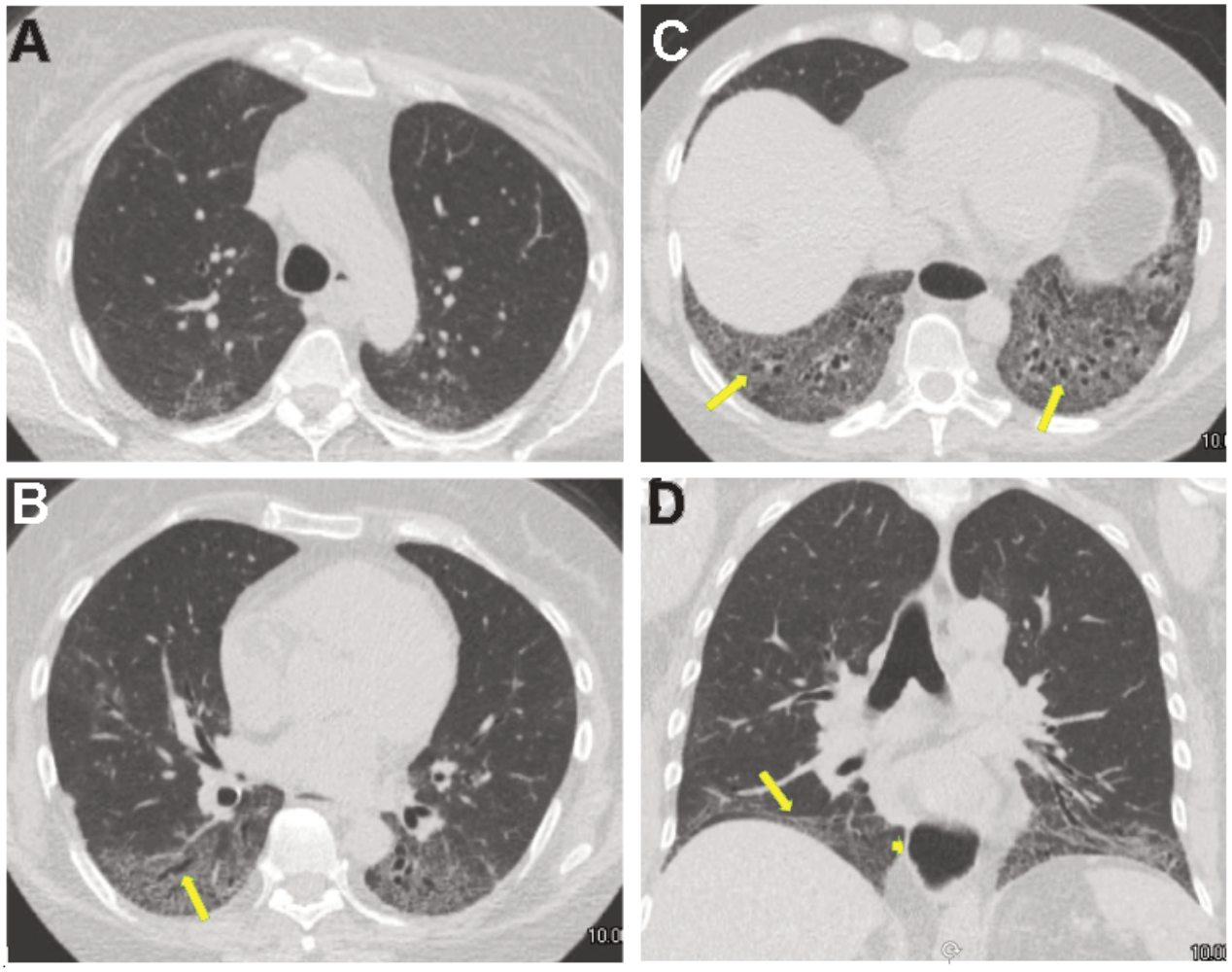

Figure 6. **HRCT scans at follow up from a patient with SSc-ILD. Axial image at the level of the aortic arch (A), axial image at the left inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal image (D). The ground glass densities in the upper lobes in A have worsened modestly. Imaging through the mid and lower lungs in B and C shows clear progression of the basilar predominant ground glass density and reticulation. Traction bronchiectasis/bronchiolectasis has substantially worsened (arrows in C), compatible with fibrotic NSIP. Note the subpleural sparing is still evident posteriorly in B and C. Coronal image shows that basilar predominant ground glass opacities, reticulation, and traction bronchiectasis have worsened. The lower lobe volume loss has clearly progressed with marked downward displacement of the right major fissure (arrow in D). Note the dilated esophagus (arrowhead in D) typical of SSc.**

than IPF who had shown progression of pulmonary fibrosis based on worsening of FVC, symptoms, or fibrotic abnormalities on HRCT within the previous 24 months, despite treatment in clinical practice [20]. In this patient population, nintedanib slowed the decline in FVC over 52 weeks, with no evidence of a differential treatment effect across diagnostic groups [20,37]. The subgroup of patients with autoimmune disease-related ILDs showed marked progression of ILD over 52 weeks [38], supporting the use of nintedanib in such patients. While the use of immunosuppression was restricted in the INBUILD trial, in the real world, combination therapy with immunosuppressive and antifibrotic agents is commonly used. Stable mycophenolate was allowed as background therapy in the SENSCIS trial [18].

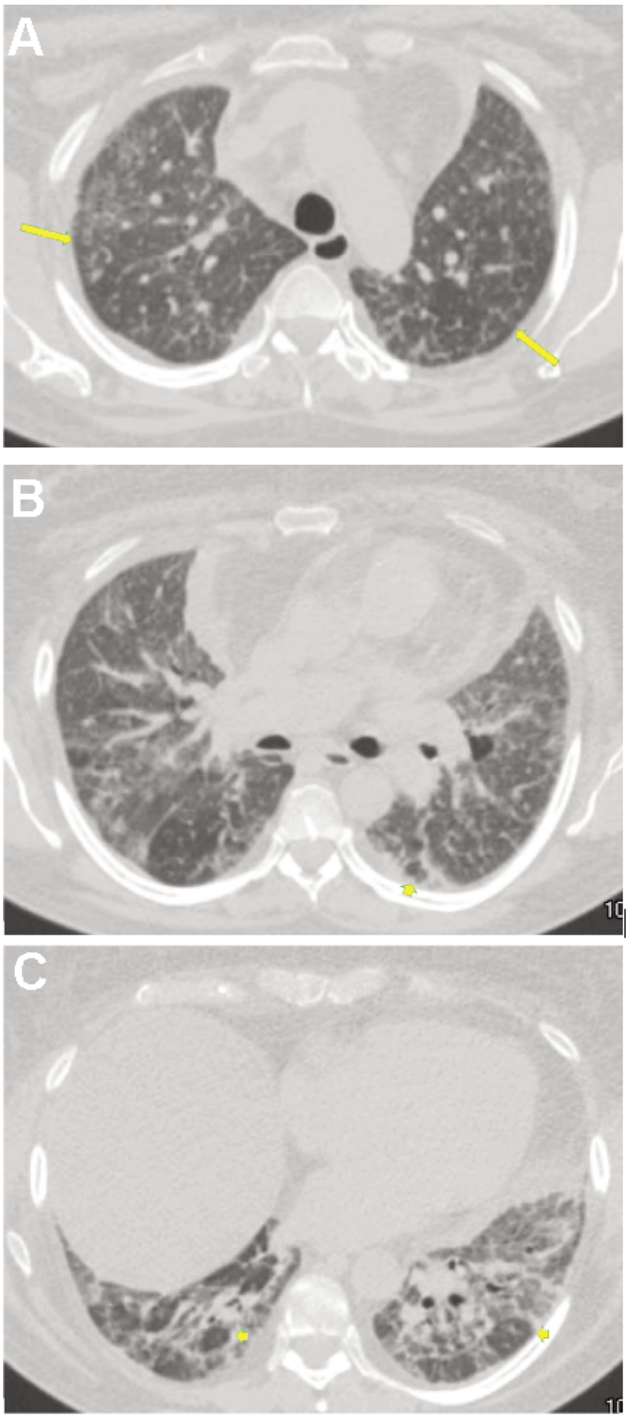

Figure 7. Axial HRCT images from a patient with anti-synthetase syndrome with myositis and ILD at the level of the aortic arch (A), below the carina (B), and just above the hemidiaphragms (C). Diffuse ground glass densities are present with areas of subpleural sparing (arrows) suggesting an NSIP pattern of lung injury. In the mid and lower lungs, more consolidative areas are noted, as well as areas of perilobular consolidation, suggesting an organizing pneumonia pattern of lung injury (arrowheads).

There is a grey area in determination of immunosuppression escalation versus addition of antifibrotic therapy in the management of progressive autoimmune disease-related ILDs. Inflammatory and fibrosing parenchymal abnormalities can influence clinical decisions. Ground glass opacifications are usually considered to represent a higher degree of cellularity and suggest that the disease is potentially more responsive to immunosuppression compared to the presence of fibrotic disease where antifibrotic therapies may be more effective. Other factors to take into consideration include the rate of disease progression, severity of lung disease, underlying autoimmune disease and extra-pulmonary symptoms, radiographic and histopathologic patterns, age, and ability to comply with therapy and monitoring [39-41]. As in our patient with SSc, when making therapeutic decisions, consideration should be given to the inflammatory versus fibrotic pattern on HRCT, extra-pulmonary symptoms and tolerability of therapies. For patients who progress despite pharmacological therapy, lung transplant should be considered [42]. Lung transplant may provide benefits on quality of life as well on survival [43]. Our first case, a patient with progressive fibrosing RA-ILD, did well after a lung transplant.

In conclusion, the diagnosis and management of ILD in patients with autoimmune diseases may be challenging and a multidisciplinary approach is recommended. Regular monitoring of patients with autoimmune disease-related ILDs is important to enable therapy to be initiated or escalated promptly if there is progression of ILD or worsening of other manifestations of disease.

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Abbreviations

NSIP: non-specific interstitial pneumonia;
MDD: multidisciplinary discussion;
anti-CCP: anti-cyclic citrullinated peptide;
CT: computerized tomography;
CTD: connective tissue disease;
DLco: diffusion capacity of the lung for carbon monoxide;
FEV_1: forced expiratory volume in one second;
FVC: forced vital capacity;
GERD: gastroesophageal reflux disease;
HRCT: high-resolution computed tomography;
IL-6: interleukin-6;
ILD: interstitial lung disease;
IPF: idiopathic pulmonary fibrosis;
LVEF: left ventricular ejection fraction;
MCP: metacarpophalangeal;
PFT: pulmonary function test;

PJP: pneumocystis jiroveci pneumonia;
RA: rheumatoid arthritis;
RV: residual volume;
SSc: systemic sclerosis
TLC: total lung capacity
UIP: usual interstitial pneumonia.

References

1. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis. A population based study. Arthritis Rheumatol 2010;62:1583-91.
2. Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med 2019;200:1258-66.
3. Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. Arthritis Rheum 2011;63:3439-47.
4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2017;69:542-9.
5. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
6. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708-719.
7. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol 2021;73:1301-10.
8. Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S, et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford) 2007;46:124-30.
9. Marie I, Dominique S, Janvresse A, Levesque H, Menard JF. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med 2012;106:581-7.
10. Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respir Med 2013; 107:890-6.
11. Andersson H, Sem M, Lund MB, Aaløkken TM, Günther A, Walle-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology (Oxford) 2015;54:1420-8.
12. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford) 2017;56:1348-57.
13. Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. J Clin Med 2020;9:277.
14. Fernández-Díaz C, Castañeda S, Melero-González RB, Ortiz-Sanjuán F, Juan-Mas A, Carrasco-Cubero C, et al. Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. Rheumatology (Oxford) 2020;59:3906-16.
15. Vadillo C, Nieto MA, Romero-Bueno F, Leon L, Sanchez-Pernaute O, Rodriguez-Nieto MJ, et al. Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: data from the NEREA Registry. Rheumatology (Oxford) 2020;59:2099-108.
16. Fujisawa T, Hozumi H, Kamiya Y, Kaida Y, Akamatsu T, Kusagaya H, et al. Prednisolone and tacrolimus versus prednisolone and cyclosporin A to treat polymyositis/dermatomyositis-associated ILD: a randomized, open-label trial. Respirology 2021;26:370-3.
17. Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med 2023;11:45-54.
18. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-28.
19. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
20. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718-27.
21. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205:e18-e47.
22. Raghu G, Remy-Jardin M, Meyers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44-e68.
23. Tomasetti S, Colby TV, Wells AU, Poletti V, Costabel U, Matucci-Cerinic M. Bronchoalveolar lavage and lung biopsy in connective tissue diseases, to do or not to do? Ther Adv Musculoskelet Dis 2021;13:1759720X211059605.
24. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB: In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000-2011. Am J Respir Crit Care Med 2016;193:1161-7.
25. Raghu G, Remy-Jardin M, Myers J, Richeldi L, Wilson KC. The 2018 diagnosis of idiopathic pulmonary fibrosis guidelines: surgical lung biopsy for radiological pattern of probable usual interstitial pneumonia is not mandatory. Am J Respir Crit Care Med 2019;200:1089-92.
26. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med 2020;8:925-34.
27. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med 2009;103:1152-8.
28. Assassi S, Shao N, Yin Z, Volkmann ER, Zoz DF, Leonard TB. Understanding diagnostic pathways in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a retrospective cohort study. Medicine (Baltimore) 2022;101:e29993.
29. Jo HE, Glaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, et al. Clinical impact of the interstitial lung disease multidisciplinary service. Respirology 2016;21:1438-44.
30. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K,

Uemura Y, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. Lancet Rheumatol 2021;3:e489-97.
31. Bauhammer J, Blank N, Max R, Lorenz H-M, Wagner U, Krause D, Fiehn C. Rituximab in the treatment of Jo1 antibody-associated antisynthetase syndrome: anti-Ro52 positivity as a marker for severity and treatment response. J Rheumatol 2016;43:1566-74.
32. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol 2020;2:e71-83.
33. Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology 2014;19:493-500.
34. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumato. 2014;66:1625-35.
35. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47:588-96.
36. Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, Manrique-Arija S, Francisco E, Aguilar-Hurtado MC, et al. Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. J Clin Med 2021;10:874.
37. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases - subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020;8:453-60.
38. Matteson EL, Kelly C, Distler JHW, Hoffmann-Vold AM, Seibold JR, Mittoo S, et al. Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial. Arthritis Rheumatol 2022;74:1039-47.
39. Goos T, De Sadeleer LJ, Yserbyt J, Verleden GM, Vermant M, Verleden SE, Wuyts WA. Progression in the management of non-idiopathic pulmonary fibrosis interstitial lung diseases, where are we now and where we would like to be. J Clin Med 2021;10:1330.
40. Castelino FV, Moua T. Detection and management of interstitial lung diseases associated with connective tissue diseases. ACR Open Rheumatol 2021;3:295-304.
41. Nambiar AM, Walker CM, Sparks JA. Monitoring and management of fibrosing interstitial lung diseases: a narrative review for practicing clinicians. Ther Adv Respir Dis 2021;15:17534666211039771.
42. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2021;40:1349-79.
43. Yazdani A, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. J Heart Lung Transplant 2014;33:514-20.

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