A practical approach to the autoimmune disease-related interstitial lung disease

Chayawee Muangchan MD.

Division of Rheumatology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract

Autoimmune diseases are heterogeneous groups of immune-mediated inflammatory diseases. However, they have multi-organ involvement, and patterns of organ complication usually present as the phenotypic trademark for each disease caused by different antibodies that recognize different sets of antigens. Pulmonary parenchyma is sometimes a target and complicated as interstitial lung disease. Autoimmune disease-related interstitial lung disease could occur at acute onset and progress rapidly or at chronic onset and insidiously progress. Host characteristics, clinical features suggesting autoimmune diseases, and serological tests help delineate the cause of ILD in the differential diagnosis.

Introduction

Interstitial lung disease (ILD) encloses a conglomeration of diseases primarily targeting the pulmonary interstitium – spaces between alveolar epitheliums and capillary endothelium. Characterized histologically into inflammation and fibrosis, it interferes with gas exchanges and results in dyspnea. Following pathogenesis, ILD can be divided into six categories. Firstly, idiopathic interstitial pneumonia, e.g., idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (I-NSIP). Secondly, autoimmune-related, e.g., systemic sclerosis (SSc), inflammatory myopathies, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren syndrome (SJS) and anti-neutrophilic cytoplasmic antibody-associated vasculitis (AAV). Thirdly, exposure-related, e.g., hypersensitivity pneumonitis, drug-induced lung injury, radiation, and postinfectious ILD. The 4th is ILD with cysts or airspace filling, e.g., lymphangioleiomyomatosis and pulmonary alveolar proteinosis. This group is also included in diffuse pulmonary lung disease. The 5th is sarcoidosis, and the 6th is miscellaneous [1]. Given the highest prevalence of IPF worldwide, autoimmune-related ILD is the second among the non-IPF ILD [2].

Three histopathological-radiological patterns frequently found in autoimmune-related ILD are usual interstitial pneumonia (UIP) characterized by HRCT-chest as a honeycombing pattern with or without traction bronchiectasis and reticulations. (Figure 1.) The next is NSIP, delineated by ground-glass opacities (GGO) with subpleural sparing (Figure 1.). The pure GGO is considered cellular NSIP, whereas the GGO with traction bronchiectasis or reticulations is fibrotic NSIP. Lastly, organizing pneumonia (OP) is specified by peripheral, subpleural, peribronchial or peribronchiolar consolidations with air bronchograms (typical pattern) or solitary focal nodule (focal pattern) or diffuse infiltrative opacities [1] (Figure 1.). Autoimmune diseases that cause ILD are a group of systemic autoimmune rheumatic diseases (SARDs), which are connective tissue disease (CTD) and AAV. CTD encompasses RA, SLE, SSc, dermatomyositis (DM)/polymyositis (PM), mixed CTD (MCTD), unclassified CTD (UCTD) and SJS [3, 4].

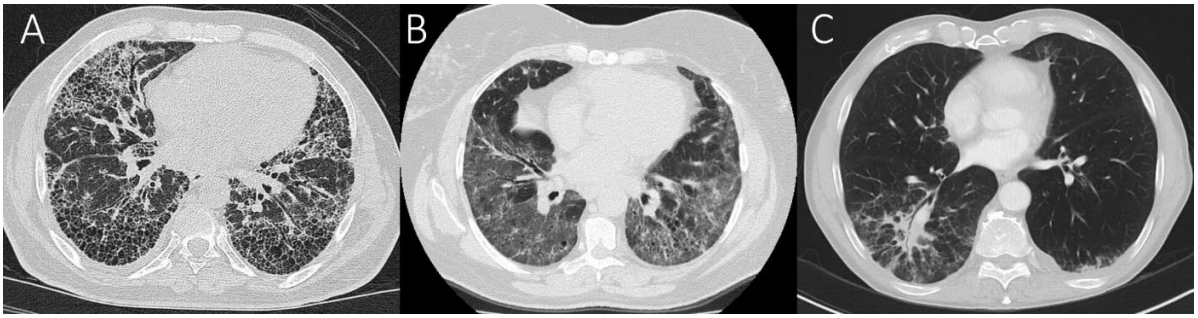

Figure 1. HRCT-chest of A. UIP shows honeycombing, B. NSIP shows GGO, and C. OP shows peripheral consolidation with air bronchograms
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AAV diseases are composed of granulomatosis with polyangiitis (GCA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [5]. The CTD, as mentioned above, and AAV diseases complicate ILD presented as an acute, subacute or chronic complication. ILD does occur before, as a concurrent course, or even later in a disease course of the CTD and AAV diseases. The clinical course can be an insidious progression, i.e., a decline in lung functions with progressive symptoms over a year in the fibrosing phenotype of ILD (F-ILD) or rapidly progressive ILD (RP-ILD) – a severe form of ILD progression that deteriorates within three months. So, it is very challenging for a consultative rheumatologist to differentiate among these entities. This concise review intends to provide an approach facing patients with dyspnea suspected of autoimmune disease-related ILD.

Epidemiology and characteristics of autoimmune disease-related ILD

Systemic sclerosis-associated ILD (SSc-ILD)

SSc is the most prevalent secondary cause of CTD-ILD. Symptomatic SSc-ILD of a major ILD extent on HRCT-chest (>20%) occurs in 35-52% of all SSc patients [6,7]. Clinicians should suggest an application of an HRCT-chest as a screening tool for SSc-ILD, resulting in ≥50% of clinically nonsignificant cases [8]. The host setting is usually a female (F: M ratio being 5:1) of late 40. Presenting dyspnea and nonproductive cough are usually subacute to chronic and progress insidiously. SSc-ILD frequently complicates early in the course of the disease, around 5 years from the onset of the Raynaud phenomenon (RP) symptom [9], accompanied by puffy fingers, scleroderma advancement, digital ischemic complications (DIC), esophageal dysmotility and reflux disease, and scleroderma renal crisis (SRC).

It is not uncommon to establish the SSc-ILD before the progression of proximal scleroderma beyond the MCP joint. Around one-fourth to one-third of patients develop ILD before the advancement of proximal scleroderma. Nearly half have ILD after the diagnosis of SSc [10]. Male gender, the diffuse cutaneous SSc (dcSSc) subset, and anti-topoisomerase-I (Scl70) positivity are the independent risks for developing the SSc-ILD [11]. It is not difficult to differentiate the SSc as an underlying CTD in patients present with well-documented proximal scleroderma. However, for the early SSc patients, there are only RP, puffy fingers, sclerodactyly, digital pitting scars, and esophageal dysmotility/ reflux disease. So, serological studies, such as an antinuclear antibody (ANA) – 95% positivity in Thais, anti-Scl70 (Sn 75%, Sp 99%), and anti-centromere (Sn 10-15%, Sp 90%), can facilitate the differential diagnosis of SSc as a cause of ILD [12, 13]. NSIP (>70%) is found more commonly than UIP (<30%). Among NSIP, fibrotic NSIP (F-NSIP) (75%) is more frequent than cellular NSIP (C-NSIP) (25%). The clinical course of SSc-ILD could be improved (30%), stable (40%), and progressive (30%). The risks of the progressive subtype are the diffuse cutaneous subset, anti-Scl70 positivity, elevated CRP, worse baseline PFT and >20% extent on HRCT-chest.

Inflammatory myopathies – associated ILD

Using clinical–pathognomic rashes, characteristic rashes, overlap features (RP, arthritis, ILD, SSc features, SLE features), serological, and pathological characters, adult autoimmune myositis or immune-mediated inflammatory myositis could be categorized into five subtypes described below [14].

1. Overlap myositis (OM)

1.1 *Anti-synthetase syndrome*: the common phenotype is PM with amyopathic to symptomatic proximal muscle weakness. The overlap features are RP, arthritis, and ILD. The group possesses anti-synthetase antibodies, e.g., anti-Jo1 and the others. This group has <5% malignancies associations.

1.2 *Anti-MDA5 syndrome*: the common phenotype is DM with amyopathic to symptomatic proximal muscle weakness. The overlap features are arthritis and ILD. The group possesses an anti-MDA5 antibody with <5% malignancy associations.

1.3 *OM with ANAs*: the common phenotype overlaps other CTDs with PM with less severe proximal muscle weakness. So, they frequently have ANA positivity as the underlying CTDs. The herald CTD features are confirmed nonparaneoplastic diseases.

1.4 *OM with DM rashes*: the common phenotype overlaps other CTDs with pathognomic DM rashes-heliotrope, Gottron papules and proximal muscle weakness varied from amyopathic to classic weakness. Serologies depend on the basic CTDs. As well as OM with ANAs, the group is a nonparaneoplastic disease.

2. Pure dermatomyositis (DM)

Pure DM is a subtype that presents with classic extensive/ refractory DM rashes with amyopathic to classic proximal with/without oropharyngeal dysphagia. It has no overlap features, so high (>50%) is associated with malignancies, especially those that pose anti-TIF1γ and anti-NXP2. Anti-Mi2 positivity is usually not associated with malignancy [15].

3. Necrotizing autoimmune myositis (NAM)

3.1 *Anti-signal recognition particle (SRP) positive NAM*

3.2 *Anti-HMGCR positive NAM*

3.3 *Seronegative NAM*

NAM has a common phenotype as PM with less severe (anti-HMGCR positivity) to classic proximal muscle weakness (anti-SRP and seronegative). It has no overlapping features. Cancer-associated has been found in statin-naïve anti-HMGCR and seronegativity groups.

4. Pure polymyositis (PM)

Pure PM is a subtype with classic subacute proximal muscle weakness of the lower extremities and progresses to the upper extremities without DM rashes and overlap features. It is considered a rare prevalence of inflammatory myopathies and has no ILD and cancer association.

5. Inclusion body myositis (IBM)

IBM is quite rare in Asia and has a distinctive weakness pattern. It presents with finger flexor weakness followed by wrist flexor, extensor weakness, and the quadriceps. It has no DM rashes, overlap features, ILD, and cancer association.

The IIM-ILD is more likely to develop in the anti-synthetase and anti-MDA5 syndrome [16]. The host setting is usually a female (F: M ratio being 5:1) of late 40-60. An Anti-synthetase syndrome usually presents with varying degrees of proximal muscle weakness, varying severity of ILD (>50%), arthritis (30%), RP (30%), mechanic's hands (40%), and fever (30%) [17]. ILD occurs >50% in this group as a presenting symptom and ranges from asymptomatic cases or chronic, insidious onset to acute respiratory distress syndrome. NSIP is the most common pathology, followed by OP and UIP. Myositis occurs more frequently in anti-Jo1 than in the non-anti-Jo1 group, but in reverse, ILD predominates in the non-anti-Jo1 group, especially in patients with anti-PL7, PL12, and EJ antibodies. In addition, the RP-ILD has been observed in the anti-PL7 and EJ antibody-positive anti-synthetase patients. Anti-Jo1 and anti-PL7/ PL12 were found to be 20-30% and 5% positivity in all IIM. In comparison, anti-OJ/EJ/KS/HA/Zo are found to be 1-3% positivity in all IIM.

An anti-MDA5 syndrome usually presents with amyopathic with distinctive DM pathognomic and characteristic rashes and arthritis (50%). ILD occurs >50% in this group and is usually more severe [18]. The overall RP-ILD in PM/DM is approximately 10% in the Asian cohort [19]. Anyway, RP-ILD in an anti-MDA5 syndrome could be as high as 50% [18]. The mortality rate in anti-MDA5-positive patients ranges from 33-66%, and over 80% of patients die from RP-ILD [20]. Anti-MDA-5 is found to be 19-

35% positivity in all DM. The clinical clues to differentiate these groups as causes of ILD are the typical rashes of DM for the anti-MDA5 syndrome and the overlap features for the anti-synthetase syndrome.

Rheumatoid arthritis – associated ILD (RA-ILD)

The RA-ILD is considered an extra-articular manifestation of RA, so it usually occurs in seropositive–anticitrullinated peptide antibody (ACPA)/ rheumatoid factor (RF) patients. It is found to be a complication in longstanding RA patients; as a result, it is not quite difficult to define RA as an underlying cause of ILD. Clinicians should look for clinical evidence of chronic synovitis and radiological changes in wrists, MCP and PIP joints. Anemia of chronic inflammation, relatively leukocytosis, thrombocytosis, hypergammaglobulinemia, and unexplained longstanding ESR/ CRP elevations. ACPA (Sn 67%, Sp 95%) and RF (Sn 69%, Sp 85%) positivity could lead to a differential diagnosis of RA. Be aware that other chronic lung diseases could have RF positivity. Likewise, in the other CTDs using HRCT-chest as a screening tool for RA-ILD, the prevalence of RA-ILD could be as high as 50%. However, the clinically significant cases are less than 5% [21, 22]. Different from the other CTDs, the common pathology in RA-ILD is UIP and airway diseases–cricoarytenoiditis/ bronchiectasis/ bronchiolitis, than the NSIP and the OP [22]. The host setting is usually a female (F: M ratio being 5:1) of late 40-50. Presenting dyspnea and nonproductive cough are usually subacute to chronic and progress insidiously. If UIP is found before the joint symptom, the CTD-UIP could be differentiated from IPF by using some HRCT-chest characteristics: anterior upper lobe sign – subpleural HC within the anterior aspect of the upper lobes, exuberant honeycombing sign – peripheral, bibasilar florid HC, and a straight edge sign – bibasilar preponderant pulmonary fibrosis forms fairly straight interface between fibrosis and normal lung on coronal view [23] (Figure 2). As methotrexate is the mainstay treatment of RA, if acute/subacute dyspnea and nonproductive cough occur early in the course of RA following using higher doses of MTX and the HRCT-chest reveals hypersensitivity pneumonitis (HP), the MTX-induced HP should be in the differential diagnosis. The prevalence of MTX-induced HP ranges from 1-2% [22].

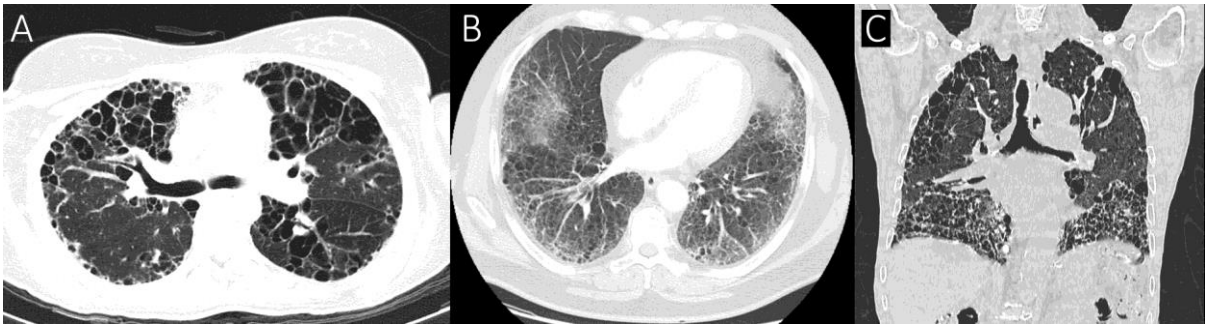

Figure 2. HRCT-chest of RA-UIP. A. an anterior upper lobe sign B. an exuberant honeycombing C. a straight-edge sign

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Sjogren syndrome – associated ILD (SJS-ILD)

SJS is an autoimmune disease affecting exocrine glands and extra glandular organs. It has two forms: primary and secondary. Secondary SJS exists with other CTDs and usually manifests with sicca symptoms. Primary SJS is a systemic autoimmune rheumatic disease (SARD) that has systemic involvement. ILD appears to be one of the systemic manifestations. Symptomatic primary SJS-ILD occurs in approximately ≤20% [24-27] and is classically considered a late complication of primary SJS. Again, using HRCT-chest as a screening tool for primary SJS-ILD could yield a higher prevalence of ILD of >60% due to the inclusion of asymptomatic cases [27]. However, ILD could occur before (20%), as a concurrent course (20%), or after the established primary SJS (60%) [25, 27, 28]. So, the cumbersome situation is the occurring ILD before the established SJS. The host setting is usually a

female (F: M ratio being 9:1) of late 50-60. Symptoms suggestive of SJS are sicca symptoms, diffuse bilateral parotid gland enlargement, RA-liked arthritis, RP, leukocytoclastic vasculitis, unexplained leucopenia, high ESR, and hypergammaglobulinemia [25, 27, 28]. ANA via Hep2 cell IFA could be positive at titer >1:320 around 80% in a fine speckled pattern. Positive RF >20 IU/mL is found in 40%, anti-Ro52 or anti-Ro60 in 50%, anti-La in 15-20%, and anti-centromere in 20% [25, 28]. The ILD pathology in order of frequency is NSIP (>50%) > UIP (20-30%) > LIP (10%) > OP (<10%); anyway, bronchiolitis could be found in 25% of cases [25-28]. Despite the link between LIP and SJS, the most prevalent ILD is still NSIP. However, the extent of primary SJS-ILD is less severe or <10% [25].

Mixed connective tissue disease-associated ILD (MCTD-ILD)

MCTD – a CTD that is a clinically combined phenotype of SSc (RP, puffy fingers/hands, esophageal dysmotility), SLE (RA-like arthritis, facial erythema, mild serositis), and PM (mild proximal muscle weakness and mild-to-moderate elevation of CPK) with a unique positivity of very high titer of ANA >1:1,600 and anti-U1RNP (Sn 100%, Sp 60%). Symptomatic MCTD-ILD at a significant extent of ILD in HRCT-chest occurs less commonly [29]. A major dyspnoeic (NHYA class 3) MCTD-ILD has been found in 10% [30]. A higher prevalence of asymptomatic MCTD-ILD has emerged using HRCT-chest as a screening tool [24]. The host setting is usually a female (F: M ratio being 9:1) of late 30-40. MCTD usually presents with RA-liked arthritis, puffy fingers and hands, esophageal dysmotility on history taking, RP on examination, paucisymptomatic or mild symptomatic hyperCKemia, and mild pleural/pericardial effusion on CXR. Symptomatic pulmonary hypertension occurs earlier during a course of MCTD or even as a presenting symptom. It might not be easy to discern pulmonary vasculitis from intimal proliferation, i.e., pulmonary arterial hypertension (PAH).

ILD at the early stage of MCTD has been found during systematic evaluation and is usually mild/ asymptomatic. PFT reveals mild pulmonary restriction (FVC 70-80% predicted). ILD extent in HRCT-chest is less than 10% [31]. NSIP (>70%) is found more commonly than UIP (<30%). Among NSIP, fibrotic NSIP (F-NSIP) (75%) is more frequent than cellular NSIP (C-NSIP) (25%) [30, 31]. MCTD-ILD is usually lessened and well-responsive, along with treatment of other organs using anti-malarial and medium-dose prednisolone as an attribute of MCTD. If the disease is in complete remission, ILD is usually not a clinical problem of MCTD. With a long period of disease duration and inadequate control of disease activity, F-NSIP could be more prominent, yielding a more restrictive pattern on PFT. However, the ILD extent in HRCT-chest in late-onset MCTD-ILD is less than 15% [31]. Anyway, a group of MCTD-ILD patients (30%) could have progressive ILD (FVC decline of ≥10% annually) [30].

Systemic lupus erythematosus associated ILD (SLE-ILD)

However, pleuritis/pleural effusion is the most common SLE-related pulmonary disease, and it is clinically found in 25-40% of cases during the disease course [32-34]. Parenchymal involvement is rarely found and occurs intercurrently with other organ flares, especially acute parenchymal complications. Acute SLE-ILD, namely acute lupus pneumonitis and diffuse alveolar hemorrhage (DAH), occur early, particularly in the first five years of the disease onset. Lupus pneumonitis is prevalent rarely, only 2-9%. Chest x-ray shows predominately unilateral/ bilateral alveolar consolidation in the lower lungs [35, 36]. DAH occurs in <5% of bilateral lower lung alveolar infiltrations as bleeding into alveoli. These two conditions occur during disease flare manifesting with fever, arthritis, mucocutaneous, hematologic, and nephritis. However, evidence of organ flares does not warrant other causes, such as infections, thrombocytopenia, and coagulopathy, which must be ruled out. Chronic SLE-ILD is quite uncommon, preferably in those with well-controlled complete remission. Around 3-8% of cases are reported to have a subclinical course and are associated with long disease duration. NSIP is the most common type, compared to UIP. So, it is not difficult to differentiate SLE as a cause of ILD as the patients already have a history of longstanding SLE.

Anti-neutrophilic cytoplasmic antibody-associated vasculitis–associated ILD (AAV-ILD)

AAV, which consists of GPA, MPA, and EGPA, apart from upper and lower airways, pulmonary parenchyma (nodules, consolidation – in GPA & EGPA, DAH – in MPA), and pleural involvements, can cause ILD [37]. AAV-ILD usually occurs in a host older than 65 years old without gender predominance and is associated with MPA more than GPA. The most frequent pathology of AAV-ILD is UIP (>70%), followed by NSIP (13-64%) [38-39]. MPO-ILD has been reported at 45%, while 23% in GPA-ILD [38, 39]. ILD could occur antedating (14-85%), simultaneously (36-67%) or after (8-21%) the onset of

systemic vasculitis [38, 39]. So, it might not be easy to define AAV as a cause of ILD if ILD occurs before the onset of systemic vasculitis. However, the term ANCA-positivity with isolated ILD (ANCA-ILD) is used in patients who develop ILD and have ANCA positivity. Anti-MPO positivity is more abundant (4-36%) than the anti-PR3 (2-4%) [38] in ANCA-ILD. Approximately one-third of these patients develop systemic vasculitis later on.

Conclusion

A schematic practical approach for the suspicion of autoimmune disease-related ILD is shown in Figure 3. When a consultant rheumatologist has to differentiate the cause of suspected autoimmune disease-related ILD, one should consider the onset, progression, pathology of ILD and the host setting. Then, look for the characteristic features of each CTD. Working up for the relevant serological testing later on and systematic evaluation as ILD might be among the other organ involvements.

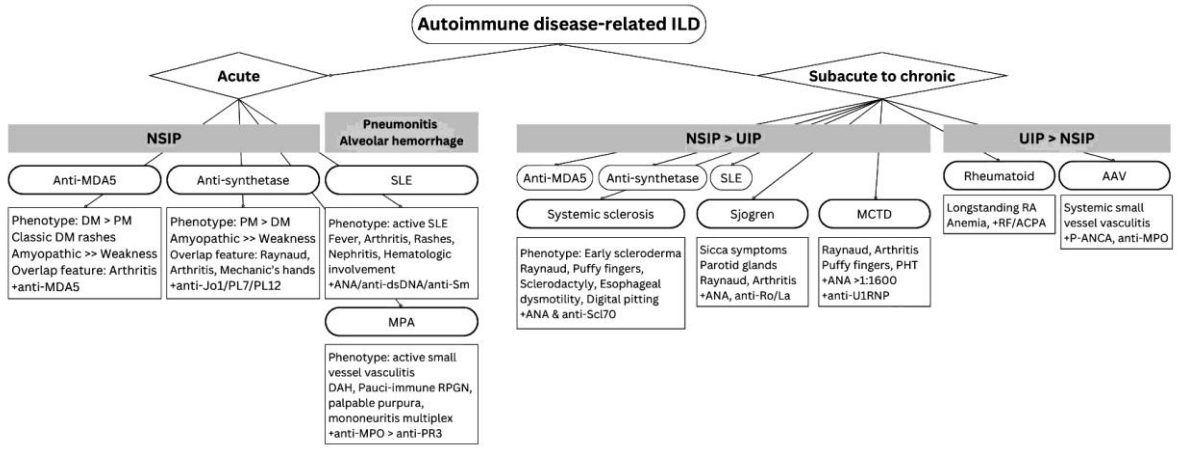

Figure 3. A schematic practical approach for autoimmune disease-related ILD

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