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## Interstitial Lung Disease in Myositis: Clinical Subsets, Biomarkers and Treatment

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### Key Words:

Idiopathic inflammatory myopathy; polymyositis; dermatomyositis; clinically amyopathic dermatomyositis; interstitial lung disease; interstitial pneumonia; NSIP; anti-synthetase antibody; anti-CADM-140 antibody; aminoacyl-transfer RNA synthetase; MDA5; IFIH1; HRCT; KL-6; SP-D; ferritin; glucocorticoid; cyclophosphamide; cyclosporine; tacrolimus; rituximab

## **Abstract**

Interstitial lung disease (ILD) is the most frequent organ involvement found in near half of myositis patients, but it reveals various clinical course and therapeutic responsiveness according to the clinical and serological subsets. Autoantibodies, as well as imaging and histopathological studies, are useful for the classification of ILD in myositis and give useful information for predicting the prognosis and determining treatment. Anti-synthetase antibodies are correlated with chronic and recurrent ILD, whereas anti-CADM-140 (MDA5/IFIH1) antibody is a marker of acute progressive ILD in clinically amyopathic dermatomyositis. Serum KL-6, SP-D and ferritin are useful biomarkers for monitoring activity and severity of ILD. As treatment, glucocorticoid is the first-line drug, but additional immunomodulating drugs are also used in refractory patients. In these drugs, cyclophosphamide and calcineurin inhibitors (cyclosporine and tacrolimus) appear to be the key drugs for the treatment of refractory myositis-ILD. Rituximab may become another candidate if these drugs are not effective.

## Introduction

Idiopathic inflammatory myositis (IIM), including polymyositis (PM)/ dermatomyositis (DM) is systemic inflammatory disorders which involve not only the muscle and skin but also many organs such as joint, heart and lung. A number of autoantibodies can be detected in sera from PM/DM patients, some of which are specific to PM/DM (known as myositis-specific autoantibodies: MSAs) or myositis overlap syndrome (known as myositis-associated autoantibodies: MAAs). These autoantibodies are closely associated with subsets, complications, reactivity to therapy and prognosis of PM/DM [1].

Interstitial lung disease (ILD) or interstitial pneumonia (IP) is the most common internal organ manifestation that affects the life prognosis of PM/DM patients. Therefore, diagnosis and evaluation of ILD is also very important to determine the treatment strategy when PM/DM is diagnosed [2-4].

Recently, two types of MSAs, namely anti-aminoacyl transfer RNA synthetases and anti-CADM-140 (MDA5/IFIH1) antibodies, have been elucidated to be closely associated with ILD in myositis. Moreover, ILD associated with these two antibodies represent completely different clinical subsets each other, providing us useful information for predicting clinical course and prognosis of ILD and for conducting the optimal treatment.

In this article, I will review recent advances and update on the clinical subsets, biomarkers and treatment of ILD associated with PM and DM.

## Epidemiologic aspect of ILD in myositis

The prevalence of ILD in myositis has been reviewed in many myositis cohorts. In earlier era, the lung involvement in PM/DM had considered to be rather rare, as only 5% was reported in a review by Frazier and Miller in 1974 [5]. However, probably the development and routine use of CT scan enables to detect early interstitial change of the lung, and then the prevalence of ILD has become increased. In the recent cohort studies (single and multicenter), the prevalence of ILD in myositis has reached to near half, ranging from 21% to 78% [6-13].

PM/DM patients accompanied ILD have poorer prognosis than those without ILD [9-11]. Prevalence of ILD seems to be similar in both PM and DM, but DM-ILD has obviously more severe course, more refractory to treatment and poorer prognosis than PM-ILD [14-16]. This may be attributed to the presence of anti-CADM-140 antibody, a poor prognostic marker of DM and amyopathic DM, which may be included in cohorts of DM-ILD as discussed later.

## Autoantibodies associated with ILD in myositis: Association between clinical and serological subsets of myositis-ILD

A number of autoantibodies can be detected in sera from IIM patients and are closely associated with clinical subsets of IIM. In these MSAs, anti-aminoacyl transfer RNA synthetases and anti-CADM-140 (MDA5/IFIH1) antibodies have been known to be closely associated with ILD in myositis. However, ILD associated with these two antibodies represent different clinical subsets with different clinical course, prognosis and response to therapy (see **Table**).

### **1) Anti-aminoacyl-transfer RNA synthetase antibodies and ILD**

Aminoacyl-transfer RNA synthetases (abbreviated as ARS or synthetase) are the enzymes which catalyze the binding of amino acids to their corresponding transfer RNAs and so there are 20 kinds of synthetases. Among MSAs, anti-synthetase antibodies are found most frequently in PM/DM patients and eight different autoantibodies reacting with different synthetases have been identified so far: anti-Jo-1 (histidyl) [17,18], anti-PL-7 (threonyl) [19], anti-PL-12 (alanyl) [20], anti-EJ (glycyl) [21], anti-OJ (isoleucyl) [22], anti-KS (asparaginy) [23], anti-Zo (phenylalanyl) [24] and anti-tyrosyl-tRNA synthetase antibodies [25]. With a few exceptions, each patient has only one of these autoantibodies, but patients show similar clinical manifestations, including ILD, myositis, arthritis, fever, Raynaud's phenomenon and mechanic's hand, called 'anti-synthetase syndrome' [26]. ILD is the most frequent extramuscular manifestation that is found in 79-95% of patients with anti-synthetase antibodies [27-31].

Although anti-synthetase-positive patients show similar clinical manifestations of anti-synthetase syndrome, some detailed clinical studies suggest that there are some differences in clinical manifestations among patients with different anti-synthetase antibodies. Anti-Jo-1 is closely associated with high prevalence of both myositis and ILD, whereas anti-OJ, anti-PL-12 and anti-KS are rather stronger association with ILD than myositis [32-35]. Anti-PL-7 antibody may be associated with PM-scleroderma overlap syndrome as well as ILD [36].

Detailed clinical features of ILD in patients with anti-synthetase antibodies have been described in several reports. The characteristics of ILD in anti-synthetase-positive patients show mostly chronic clinical course but subacute course is also found [37]. In one third to half patients with anti-synthetases, ILD precedes the development of myositis [29,30]. Yoshifuji *et al* reported the usefulness of anti-synthetase in clinical course prediction of ILD with IIM patients [29]. This retrospective study analyzed 74 patients with myositis in whom 41 had ILD. Any of anti-synthetases were detected in 28% (21/74) of whole IIM patients. ILD was accompanied in 41 (55%) of 74 IIM patients and anti-synthetases was found in 49% (21/41) of IIM-ILD patients. Anti-synthetase-positive patients had significantly higher frequency of ILD (95%) than negative patients (40%), and ILD of the most positive patients were diagnosed at the same time or before developing myositis. ILD of patients with anti-synthetases showed a better response to initial glucocorticoid therapy

but revealed significant higher recurrence than those without anti-synthetases. As the result, the 2-year prognosis of pulmonary function was not different between the two groups of each anti-synthetases status. The detection of anti-synthetases may be useful to predict the late-onset myopathy in ILD-preceding patients and to predict the clinical course of ILD in myositis patients.

Anti-/SS-A/Ro antibody is detected in various connective tissue diseases but anti-Ro52 antibody is categorized in one of MAAs. Isolated anti-Ro52 in myositis patients is often correlates with anti-Jo-1 antibody [38-40]. Anti-SS-A/Ro antibody in patients with anti-synthetase syndrome seems to be associated with the development of a more severe ILD [39] and a more frequent association with fibrosis of lung and a less efficacy of immunosuppressive therapy [40].

The production of disease-specific autoantibodies may closely correlate to pathogenic mechanisms of inflammatory myopathy. Patients with antibodies to different synthetases show the same clinical syndrome. This fact strongly suggests that the immune response to molecules with analogous functions leads a similar clinical syndrome. However, the pathophysiologic role of anti-synthetase antibodies in myositis and/or ILD remains to be clarified. There are several reports that suggest a possible pathogenic role of anti-synthetases.

In an animal model, immunized mice with murine Jo-1 antigen generated specific B and T cells targeting species-specific epitopes of murine Jo-1 and developed a phenotype consistent with muscle and lung inflammation resembling features of human anti-synthetase syndrome [41]. Sera from anti-Jo-1-positive PM-ILD patients induced a significant effect on the expression of ICAM-1 from human lung endothelial cells [42], although autoantibodies themselves might not be the endothelial cell-activating factor since purified IgG did not induce ICAM-1 expression.

Recent reports demonstrate that certain synthetase molecules (histidyl-, asparaginyl-, and seryl-tRNA synthetases) and their proteolytic fragments have chemokine-like activities against inflammatory cells such as CD4+ and CD8+T cells, and activated monocytes and immature dendritic cells [43]. Mononuclear cells expressing chemokine receptors such as CCR3 and CCR5 infiltrate in muscle tissues of myositis patients but not in normal muscle, supporting the results that histidyl- and asparaginyl-tRNA synthetases activate CCR5+ and CCR3+ cells, respectively [43]. These findings indicate that the liberation of autoantigenic synthetases from damaged tissues may recruit inflammatory mononuclear cells and perpetuate the inflammation process of myositis and ILD, and also induce autoimmune responses to autoantigens.

## **2) Anti-CADM-140 (MDA5/IFIH1) antibody and ILD**

Amyopathic DM (ADM) and clinically ADM (C-ADM) is defined as the disorder which shows the typical skin manifestations of DM but no or little evidence of clinical myositis [44,45]. It is known that C-ADM patients mostly in Asian countries frequently develop life-threatening

acute progressive ILD [46-50].

Until recently it was thought that MSAs could not be detected in patients with C-ADM and this appeared to be a characteristic feature. In 2005, however, Sato *et al* reported the identification of a specific autoantibody in C-ADM patients [51]. They screened the sera of 314 patients and controls by <sup>35</sup>S-methionine-labeled protein immunoprecipitation and immunoblotting techniques using K562 cells, and 8 of 15 patients with C-ADM immunoprecipitated a 140kD protein. This newly identified autoantibody was named as anti-CADM-140 antibody. In 15 patients with C-ADM, 13 developed ILD and 5 were acute ILD. In the 5 patients with acute ILD, 4 had anti-CADM-140 antibody. Later, the presence of anti-CADM-140 and the association with C-ADM-ILD have been confirmed worldwide. The antibody can be detected exclusively in DM (11-26%) or C-ADM (50-73%) [52-56].

Nakashima *et al* reported the characteristics of anti-CADM-140-positive patients [52]. In screening of 192 patients with various CTD, 13 revealed to be positive with anti-CADM-140 antibody. All anti-CADM-140-positive patients were DM either typical DM (2 cases) or C-ADM (11 cases), and 9 (69%) patients had fever >38°C, while 12 patients (92%) had ILD and 7 (54%) developed acute progressive ILD. Life prognosis was significantly poorer in anti-CADM-140-positive patients than in anti-CADM-140-negative DM patients, and 6 (46%) died of respiratory failure within 6 months from the onset of disease. Interestingly, the serum ferritin concentrations in 11 of anti-CADM-140-positive patients were already elevated within one month of their admission with significantly high frequency in comparison with anti-CADM-negative DM patients (85 vs. 33%; p=0.005). Moreover, the serum ferritin level correlated to the activity of ILD in anti-CADM-140-positive patients.

ILD in anti-CADM-140-positive patients was correlated abnormalities in serum hepatobiliary enzymes and interleukin-18, which worsened in accordance with ILD and ferritin levels [57,58]. Thus, the anti-CADM-140 antibody appeared to be associated with macrophage activation syndrome developed in C-ADM and intractable acute ILD.

The target autoantigen of anti-CADM-140 antibody was identified as melanoma differentiation-associated gene 5 (MDA5), also known as interferon induced with helicase C domain protein 1 (IFIH1) [52,59]. MDA5/IFIH1 is one of the retinoic acid-inducible gene-I (RIG-I)-like receptors, which are involved in the recognition of viral RNAs and play an important role in innate immune responses. RIG-I and MDA5/IFIH1 are able to interact with viral RNA and mediate signaling pathways leading to the expression of type I interferon and inflammatory cytokines.

Finding MDA5/IFIH1 as the autoantigen specifically recognized by one of DM-specific autoantibodies is strikingly interesting, because many reports have suggested the possible association between myositis and viral infections [60-62], in particular Coxsackie B virus belonging to the picornaviruses that are targeted by MDA5/IFIH1. To increase our understanding of the pathophysiology of acute ILD accompanied with C-ADM and to develop more effective therapy, whether anti-CADM-140 antibody and its target antigen MDA5/IFIH1 have pathogenic roles in ILD and C-ADM should be elucidated.

## Radiological and histopathological findings of ILD in myositis

In histopathological analysis by VATS or TBLB, nonspecific interstitial pneumonia (NSIP) is the most frequent histological pattern of ILD in myositis, but usual interstitial pneumonia (UIP), organizing pneumonia (OP) and diffuse alveolar damage (DAD) can also be found though less frequent [14,63-65]. These histological findings are partially but not always associated with the underlying disease (PM or DM), clinical course (acute or chronic) and autoantibody profiles. While NSIP is widely found in both PM and DM, UIP is associated with chronic ILD (both PM and DM), and DAD is characteristically found in acute refractory ILD in DM and C-ADM. OP shows a good response to glucocorticoid therapy.

High resolution computed tomography (HRCT) scanning of chest is a most sensitive technique to detect ILD, and provide information for prognosis and response of treatment.

Typical HRCT findings in myositis-associated ILD include ground glass opacities (GGO), micronodules, linear and reticular opacities, peribronchovascular or subpleural consolidation, irregularity of interface, and traction bronchiectasis [15,46,65,66] (see **Figure**). These findings are compatible with NSIP. Honeycombing pattern suggesting UIP is also found in ILD-myositis but with lower frequency.

Recent studies suggest characteristics of HRCT findings in two myositis/ILD-associated autoantibodies. Watanabe *et al* reported the HRCT and pathological findings in 13 ILD cases with anti-synthetase syndrome but without clinical myositis [67]. Pleural irregularities and/or prominent interlobular septa, GGO, reticulation and traction bronchiectasis were the major findings, while honeycombing was not found in any case. Although most of these cases showed histological NSIP if lung biopsies were applied, even in cases with pathological diagnosis of UIP, HRCT findings were not compatible with a typical UIP pattern showing honeycombing.

Tanizawa *et al* described HRCT findings of ILD in DM/C-ADM with anti-CADM-140 antibody [68]. GGO, non-septal linear or plate-like opacity and consolidation were the common findings in ILD of both antibody-positive and negative DM. However, intralobular reticular opacities (abnormal thickening of intralobular interstitial tissues) found in the antibody-negative ILD was significantly less in the positive ILD. Moreover, lower consolidation/GGO pattern (lower peripheral or peribronchovascular consolidation or GGO) and random GGO pattern (random peripheral GGO) were mainly found in anti-CADM-140-positive patients, whereas lower reticulation pattern (lower peripheral or peribronchovascular reticulation) was the main finding of anti-CADM-140-negative patients.

The latter HRCT pattern is compatible with NSIP and likely to that of anti-synthetase-positive ILD, while three patients who were negative for both anti-CADM-140 and anti-synthetases showed lower reticulation pattern as well. Thus, HRCT of anti-CADM-140-positive DM/C-ADM-ILD is characterized by lower consolidation/GGO and random GGO patterns and the absence of intralobular reticular opacities, which are different from typical NSIP patterns (see **Figure**).

Lower reticulation pattern is consistent with NSIP and likely to that of anti-synthetase-positive ILD. On the other hand, lower consolidation/GGO and random GGO patterns in anti-CADM-140-positive ILD are hard to interpret because the pathological approach is usually difficult in early stage of the disease. Lower consolidation/GGO may represent OP or localized DAD [68]. These findings and the absence of lower reticulation and intralobular reticular opacities in anti-CADM-140-positive ILD may suggest a lower prevalence of pathological NSIP.

## **Biomarkers of ILD in myositis**

There are no specific serum biomarkers for myositis-associated ILD. Nevertheless, certain serum markers predicting activity of ILD should be necessary, since a correlation is often not recognized between activities of myositis and ILD. HRCT of lung is the most valuable and sensitive method to detect and predict the activity of ILD, but frequent examination should avoid because of the risk for high radiation exposure by CT. Several biomarkers that may reflect inflammatory activity of lung have been utilized.

### **1) KL-6 and SP-D**

KL-6 (Krebs von den Lungen-6) is a mucin-like glycoprotein expressed in type II alveolar epithelial cells. Since serum level of KL-6 increases by reflecting hyper-expression of KL-6 producing cells and alveolar injury in ILD, its detection is useful as a serologic biomarker for diagnosis and monitoring of ILD. Several studies suggested the usefulness of KL-6 in disease activity, therapeutic response and prognosis of myositis-ILD [69-74]. Satoh et al demonstrated that high serum level (>1000 U/ml) of KL-6 was a poor prognostic factor in 152 idiopathic IP and 67 connective tissue disease-associated ILD including 16 PM/DM patients before treatment [72].

SP-D (Surfactant protein-D) is a lung-specific surfactant lipoprotein secreted from type II alveolar epithelial cell. Serum level of SP-D reflects the activity of certain lung diseases such as ILD and pulmonary alveolar proteinosis [71,73]. Comparing with KL-6, SP-D appears to have same specificity but lower sensitivity [71].

### **2) Ferritin**

Recent studies suggest serum ferritin level as a marker for severity of acute progressive ILD in DM and C-ADM patients [52,57,75,76]. The serum ferritin concentrations in anti-CADM-140-positive patients are already elevated from early stage of the disease with significantly high frequency in comparison with antibody-negative DM patients even if ILD is not worsened [52]. Moreover, the serum ferritin concentration correlates to the activity of ILD in anti-CADM-140-positive patients.

Gono *et al* showed that serum ferritin level before initial treatment in acute or subacute ILD in DM patients was significantly higher (mean 790 ng/ml) than in chronic ILD (188 ng/ml) and non-ILD patients (160 ng/ml) [75]. Patients with ferritin level more than 1500 ng/ml showed significantly poorer prognosis than those with less than 1500 ng/ml. They also reported that serum ferritin was significantly elevated in patients with anti-CADM-140 (MDA5)-positive acute ILD and correlated with prognosis and disease activity [57,76].

### **3) Titers of autoantibodies**

It is not clarified whether myositis-specific autoantibodies are directly involved in pathophysiologic mechanisms of myositis and ILD. Correlation between titers of such autoantibodies and activity of myositis or ILD is controversial. There are several reports that anti-Jo-1 antibody titers correlated with activity of myositis as well as lung [77], and anti-CADM-140 titer disappeared after intensive treatment of ILD in ADM patients [78]. However, these changes of antibody titers are modest, and further studies will be necessary for conclusion.

## **Treatment**

Regarding the therapy of ILD in myositis, glucocorticoids are the empirical first-line drug, and additional immunosuppressive agents are often used as the second-line drugs in cases of refractory disease. However, these therapies are not based on high levels of evidence (i.e. randomized controlled trials) but based on long-term experiences, retrospective studies and small-scale case series or case reports. Since ILD is a progressive and fatal disease and glucocorticoids have been established as the standard therapy, it is difficult to conduct placebo-controlled prospective trials.

### **1) Glucocorticoids (GC)**

Oral high-dose GC (more than 1mg/kg/day of prednisone) or pulse therapy of methylprednisolone (1000mg iv for 3days) is the first-line therapy of ILD in myositis. Roughly half of ILD in myositis is effective to the initial GC therapy [14,29,37,79]. However, acute ILD, especially rapid progressive ILD in anti-CADM-140-positive DM/C-ADM is usually not responsive to GC alone [51-56].

Fujisawa *et al* reported 28 ILD with myositis (16 PM and 12 DM) and their difference in

efficacy of treatment [14]. GC alone achieved a favorable response in 6 patients (37.5%) with PM-ILD but in only one (8.3%) with DM-ILD. Overall 2.5-year survival in DM-ILD was 58% and 5-year survival in PM-ILD was 81%. In the similar study by Nawata *et al*, when ILD was classified into two groups according to serum creatine kinase (CK) levels (high CK or normal CK), the normal CK group showed significantly more resistant to GC therapy and poorer prognosis than those with high CK (one-year survival 31% vs. 89%) [79].

Although these studies have not reported the autoantibody status, GC-refractory ILD with DM (not PM) or normal CK patients may represent the characteristic features of patients with anti-CADM-140 antibody, who have reported to have treatment resistance and poor prognosis. It has been obvious that the prognosis of initial GC-resistant ILD patients is not improved even if immunosuppressive drugs add after exacerbation of respiratory symptoms. The efficacy of GC as the initial therapy of ILD is limited, nevertheless GC is still the mainstay of therapy.

## **2) Cyclophosphamide (CYC)**

CYC, oral or intravenous pulse (IVCYC), is commonly used in acute or refractory ILD, and has demonstrated its efficacy in several case series and small-scale open label trials [7,80-82]. Yamasaki *et al* reported 17 cases of refractory ILD in myositis who treated with IVCYC (300-800mg/m<sup>2</sup> at least 6 times every 4weeks) and showed significant improvement in dyspnea, pulmonary function and HRCT findings [82].

CYC is also used in combination with other immunosuppressive drugs in refractory ILD [83,84]. Kameda *et al* reported the efficacy of IVCYC in combination with GC and cyclosporine in 10 DM patients with acute ILD [84]. Although 5 patients who received the combination therapy died of respiratory failure within 3 month, the mortality rate tended to become lower than in the historical control in which 9 out of 12 patients died despite high dose GC with or without a choice of CYC, cyclosporine or azathioprine.

## **3) Calcineurin inhibitors**

Calcineurin inhibitors such as cyclosporine and tacrolimus targeting activated T cells by inhibiting calcineurin and nuclear translocation of NF-AT may become the cornerstone for the treatment of ILD in myositis.

### **a. Cyclosporine (CSP)**

There are several retrospective or open-label studies to analyze the efficacy of CSP in PM/DM-ILD [14,37,85,86,79]. Nagasaka *et al* reported a multicenter retrospective analysis of 38 cases with acute ILD in PM/DM [86]. In this study, ILD in PM (9 cases) and chronic ILD in DM (5 cases) showed good efficacy of CSP and good prognosis, whereas patients with acute IP in DM showed poor response and poor prognosis (7 out of 17 dead). Moreover, in a further analysis of 32 cases with acute DM-ILD, 9 out of 13 cases starting CSP within 2 weeks from initial GC were survived (survival rate 69%), whereas all 17 cases receiving only GC more than 2 weeks as the initial therapy died within 9 months from the therapy. In the

retrospective study by Kotani *et al* analyzing the efficacy of CSP in 16 DM cases with acute or subacute ILD, 9 cases treated initially with GC and CSP (mean interval 3.8 days) appeared to show good prognosis (only one dead), whereas 4 out of 7 cases (57%) in whom CSP was added when initial GC not effective (mean interval 20.0 days) died of respiratory failure related to ILD [87].

Monitoring of serum CSP concentration is important for achieving maximal efficacy and for reducing toxicity. Trough level (C0) and 2-hour post-dose blood concentration (C2) are correlated with the therapeutic effects [88,89]. They also suggest that once daily preprandial administration of CSP, rather than twice daily, may be beneficial in DM patients with progressive ILD [89]. These studies, although small scaled retrospective analyses, suggest the effectiveness of early intervention and tight control by CSP in combination with GC in the treatment of refractory myositis-ILD.

#### **b. Tacrolimus (TAC)**

TAC is another calcineurin inhibitor and has 100-fold more potent to inhibit T cell activity comparing with CSP. Recently TAC has been utilized in refractory ILD in myositis patients as well as CSP. Several case series and retrospective studies show the efficacy and tolerability of TAC in patients with PM/DM-ILD refractory to CSP [86,90-92]. TAC appears to be more effective in ILD of anti-synthetase syndrome [91,92]. Wilkes *et al* retrospectively analyzed 13 anti-synthetase-positive patients treated with TAC and showed its efficacy both for refractory ILD and myositis being well tolerated [92].

### **4) Rituximab**

Rituximab is a biologic agent of chimeric monoclonal anti-CD20 antibody that targets B cell. Recently its potential usefulness has been demonstrated in various autoimmune diseases, and several case reports and case series of rituximab have also been reported in myositis-ILD [93-95]. Sem *et al* reported 11 refractory ILD in anti-synthetase syndrome patients treated with rituximab and showed that rituximab stabilized and/or improved the ILD in 7 of 11 patients [93]. Rituximab reduced the serum titer of anti-Jo-1 antibody but the effect was modest.

### **5) Other immunomodulating therapies**

#### **a. Methotrexate (MTX)**

Although MTX, inhibitor of folic acid and purine metabolisms, is widely used in treatment of refractory PM/DM, there is no obvious evidence on myositis-ILD. The use of MTX in ILD is controversial because there are patients that respond favorably to this treatment but the risk for idiosyncratic drug-induced ILD is reported on the other hand. Particular care should be taken if using MTX for ILD in myositis.

#### **b. Azathioprine (AZT)**

AZT has been widely used in myositis and ILD as the second-line immunomodulating drug, but its efficacy is modest. AZT may be useful as a maintenance therapy for the control of

ILD after CYC.

**c. Mycophenolate mofetil (MMF)**

In a few case series studies, the potential efficacy of MMF has been shown in stabilization of progressive ILD and reducing GC dose in ILD patients with connective tissue diseases including PM/DM [96-97].

**d. Intravenous immunoglobulin (IVIG)**

The efficacy of IVIG has been demonstrated in muscular symptoms of refractory DM and PM, but the usefulness in ILD associated with myositis is uncertain. One case series of 5 patients with severe ILD reported a potential usefulness as a salvage therapy [98].

**e. Anti-cytokine biologics**

The use of anti-TNF [99,100] and other biologics (including tocilizumab [101] and anakinra [102]) have been reported in some case reports and case series and in a randomized pilot trial [100]. However, all of them focused on severe or refractory myopathy but not on ILD. They appear to be sometimes effective on myositis but some reports suggest no effect or even worsening muscle symptoms [99]. Their efficacy on ILD is not discussed. Experience of anti-cytokine therapies on myositis-ILD should be collected and carefully investigated.

## **Conclusion**

ILD is the most frequent extra-muscular organ involvement and the most important prognostic factor of IIM, but it reveals various clinical course and therapeutic responsiveness according to the clinical and serological subsets. Autoantibodies, as well as imaging and histopathological studies, are useful for the classification of ILD in myositis, and give us useful information for predicting the prognosis and determining therapeutic strategy. Routine examination of anti-CADM-140 antibody and anti-synthetase antibodies except for anti-Jo-1 are not available so far, since these antibodies can only be detected by complicated immunoprecipitation techniques. Quantitative methods to detect these MSAs are now developing and will be available in near future.

As treatment of ILD in myositis, GC is still the first-line drug and various immunomodulating drugs are also frequently used in refractory patients. In these drugs, CYC (especially IVCYC) and calcineurin inhibitors (CSP and TAC) appear to be the key drugs for the treatment of refractory ILD in myositis. Rituximab may be another candidate if these drugs are not effective. However, there are no large-scale, randomized clinical trials to guarantee the efficacy and safety of these drugs. Although it may be difficult to conduct placebo-controlled trials in such progressive and fatal condition, the construction of evidences should be necessary to achieve the best management of intractable disease like ILD.

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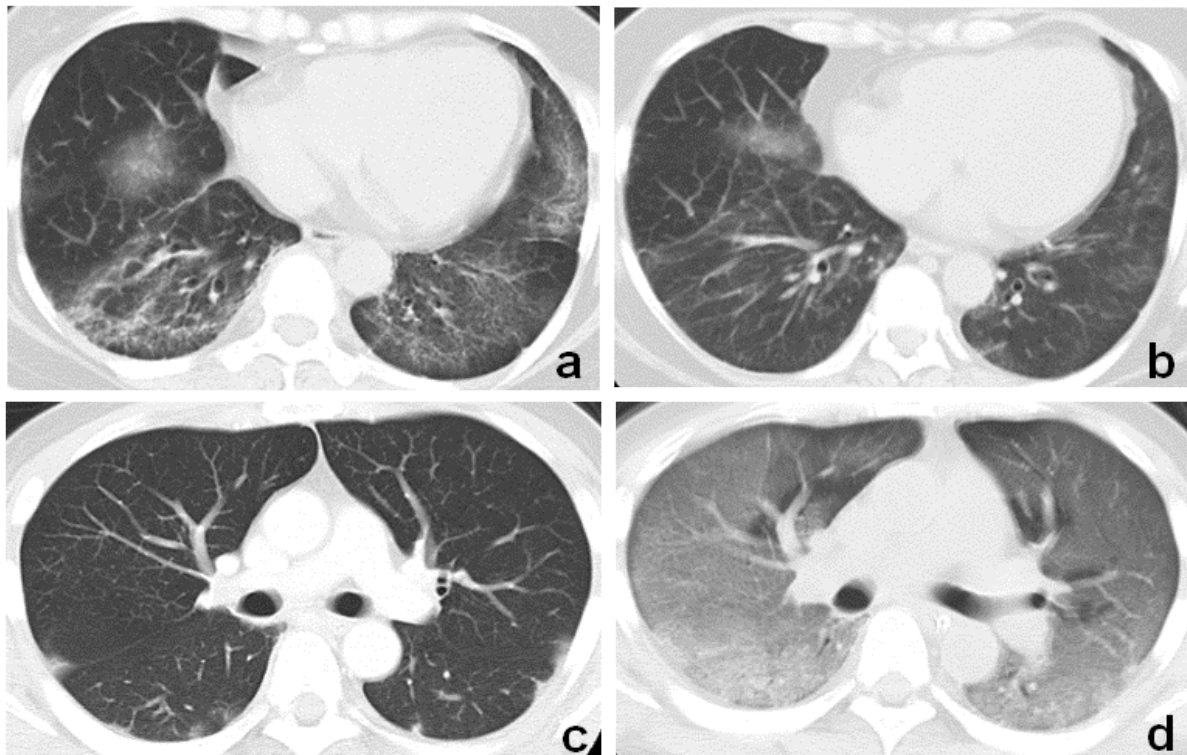
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**Table. Two subsets of ILD in myositis defined by autoantibodies**

|                       | Anti-synthetase-related ILD                                     | Anti-CADM-140-related ILD              |
|-----------------------|-----------------------------------------------------------------|----------------------------------------|
| Target antigen        | aminoacyl-tRNA synthetases<br>(8 types)                         | MDA5/IFIH1                             |
| Frequency in myositis | ~30% in whole PM/DM                                             | ~10-20% in DM<br>~50-70% in C-ADM      |
| Frequency of ILD      | 70-95%                                                          | 50-90%                                 |
| Type of ILD           | chronic or subacute                                             | acute progressive                      |
| Histopathology        | mostly NSIP<br>sometimes UIP and OP                             | NSIP? (early stage)<br>DAD (end stage) |
| HRCT pattern          | basilar GGO<br>reticular or linear opacity<br>rare honeycombing | lower and random GGO/<br>consolidation |
| Prognosis             | fair but recurrent                                              | poor                                   |
| Response to treatment | fair                                                            | poor                                   |
| Recommended therapy   | GC +CSP or TAC                                                  | GC+IVCYC+CSP                           |



**Figure.** Radiographic imaging of CT in patients with myositis–interstitial lung disease having antisynthetase (a and b) and anti-CADM-140 antibody (c and d). A typical CT image shows basilar ground glass opacities (GGOs), reticular opacities, and traction bronchiectasis in a 47-year-old woman with dermatomyositis (DM) and anti-PL-7 antibody (**a**). A CT image of the same patient 1 year later shows significant improvement achieved by treatment with high-dose corticosteroids (**b**). CT image shows random consolidation/GGOs in subpleural region in a 44-year-old man with DM and anti-CADM-140 antibody at diagnosis (**c**). One month later, the patient developed severe respiratory failure and died despite treatment. Diffuse GGOs and consolidation were extended in the whole lung (**d**).