

Biomarkers and Autoantibodies of Interstitial Lung Disease with Idiopathic Inflammatory Myopathies

Hajime Yoshifuji

Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

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ABSTRACT: Various autoantibodies are seen in idiopathic inflammatory myopathies. Among myositis-specific antibodies, anti-aminoacyl-tRNA synthetase and anti-melanoma differentiation-associated protein 5 (MDA5) antibodies are associated with interstitial lung disease (ILD). Anti-MDA5 antibodies are associated with dermatomyositis (DM) or clinically amyopathic DM complicated with rapidly progressive ILD. In anti-MDA5-positive patients, a random ground-glass attenuation pattern is a characteristic finding of ILD in chest high-resolution computed tomography. Conversely, anti-aminoacyl-tRNA synthetase antibodies are not associated with rapidly progressive ILD but with chronic ILD. DM or clinically amyopathic DM patients with anti-MDA5, and characteristic high-resolution computed tomography findings are highly likely to have devastating ILD and need aggressive treatment.

KEYWORDS: dermatomyositis, interstitial lung disease, computed tomography, aminoacyl-tRNA synthetase, melanoma differentiation-associated protein 5

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CORRESPONDENCE: yossii@kuhp.kyoto-u.ac.jp

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Introduction

The term idiopathic inflammatory myopathy (IIM) appeared in Bohan and Peter's¹ review in 1975. They classified IIM into the following five subgroups: polymyositis (PM), dermatomyositis (DM), cancer-associated myositis (CAM), juvenile DM, and overlap syndrome (OS); these terms are not identical to the original names given by Bohan and Peter because they were subsequently modified by Euwer and Sontheimer.² Because various autoantibodies have been detected, IIM is considered an autoimmune disease whose main target organs are muscles and skin. In 1991, Dalakas³ suggested incorporating inclusion body myositis (IBM) in the IIM group. However, it is still controversial whether IBM is an autoimmune disease. Pluk et al.⁴ reported anti-cytosolic 5'-nucleotidase 1A antibodies found in 33% of sporadic IBM patients. However, recently, Herbert et al.⁵ reported that anti-cytosolic 5'-nucleotidase 1A antibodies are detected in other autoimmune diseases and are not specific to IBM. In 1993, Euwer and Sontheimer² suggested adding amyopathic DM (ADM) to the IIM group. ADM lacks muscle symptoms but is characterized by a pathognomonic skin rash of DM and is considered an established category associated with DM.

Approximately 50% of IIM patients are complicated with interstitial lung disease (ILD), and having ILD is related to

poor prognosis. In this review, several biomarkers and autoantibodies of ILD complicated with IIM are introduced, and their application to diagnosis and treatments is discussed.

Autoantibodies in IIM

Autoantibodies detected in IIM are divided into two categories, myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA). MSA and MAA are associated with specific symptoms and clinical features (Table 1).^{6–8} The association between MSA and symptoms was reported by Love et al.⁹ They investigated the association between MSA and clinical features in 212 adult IIM patients and found that anti-aminoacyl-tRNA synthetase (ARS) antibodies are associated with anti-synthetase syndrome, while anti-signal recognition particle (SRP) antibodies are associated with refractory PM, and anti-Mi-2 antibodies are associated with a certain skin rash of DM. They suggested a new approach to classify IIM using MSA. The concept of classification of IIM using MSA has been supported by the discoveries of anti-melanoma differentiation-associated protein 5 (MDA5) antibodies associated with ADM¹⁰ and anti-transcription intermediary factor 1- γ/α (TIF1- γ/α) antibodies associated with CAM.¹¹ When we consider the classification of IIM using MSA, it is notable that MSA are mutually exclusive and generally do not

**Table 1.** Autoantibodies detected in idiopathic inflammatory myopathies.

GROUP	AUTOANTIBODY	AUTOANTIGEN	FREQUENCY [REF.]	CLINICAL FEATURE
Myositis-specific antibodies	Anti-ARS	Aminoacyl-tRNA synthetase (ARS)	25–42% of all myositis [6–7]	PM, DM, ILD, Raynaud's phenomenon, Polyarthritides, High fever, Mechanic's hand
	Anti-Mi-2	Nucleosome remodeling and deacetylase complex (NuRD)	4–10% of all myositis [6–8]	DM, JDM, V-sign, Shawl sign
	Anti-SRP	Signal recognition particle (SRP)	3–10% of all myositis [6–8]	PM, Necrotizing myositis, Severe and rapidly progressive myositis
	Anti-TIF1- γ/α	Transcription intermediary factor 1- γ/α (TIF1- γ/α)	20–29% of DM [6, 8]	CAM, DM, JDM
	Anti-MDA5	Melanoma differentiation-associated protein 5 (MDA5)	12–13% of DM [27–28]	CADM, DM, Severe and rapidly progressive ILD
Myositis-associated antibodies	Anti-cN1A	Cytosolic 5'-nucleotidase 1A (cN1A)	33–37% of IBM [3, 4]	IBM
	Anti-U1-RNP	U1-ribonucleoprotein (U1-RNP)	6–10% of all myositis [7–8]	Overlap syndrome, MCTD, Raynaud's phenomenon, ILD, PAH
	Anti-PM/Scl	PM/Scl-100, PM/Scl-75	3–10% of all myositis [7–8]	PM-SSc overlap syndrome
	Anti-Ku	Components of DNA-dependent protein kinase (Ku70/Ku80)	2% of all myositis [7]	Overlap syndrome

Abbreviations: CADM, clinically amyopathic dermatomyositis; CAM, cancer-associated myositis; DM, dermatomyositis; IBM, inclusion body myositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PM, polymyositis; SSc, systemic sclerosis.

overlap. In the analysis of IIM patients positive for MSA by Love et al.⁹, each patient had a single type of MSA.

Distinct from MSA, MAA are not specific to IIM patients. Anti-U1-RNP antibodies are major MAA and detected in patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), PM, and mixed connective tissue disease. Anti-PM/Scl antibodies¹² are also seen in various connective tissue diseases, such as PM-SSc OS, PM, DM, SSc, SLE, and undifferentiated connective tissue disease (UCTD). In our analysis of six anti-Ku-positive patients, two had PM-SLE OS, two had SLE, one had PM, and one had UCTD. Taken together, MAA can be seen in patients with myopathy complicated with other connective tissue diseases.

Biomarkers Associated with ILD in IIM

Serum lactate dehydrogenase, KL-6, and surfactant protein D. Serum lactate dehydrogenase (LDH), KL-6, and serum surfactant protein D (SP-D) reflect lung damage and are universal activity markers of ILD and can also be biomarkers of ILD complicated with IIM. Serum LDH is a classical activity marker of ILD, although it is less specific for lung lesions than serum KL-6 and SP-D. KL-6 is a mucin-like high molecular weight glycoprotein expressed in type II alveolar pneumocytes and bronchiolar epithelial cells. Fathi et al.¹³ reported that the serum KL-6 level was significantly higher in PM/DM patients with ILD than in PM/DM patients without ILD (sensitivity: 83% and specificity: 100%) and serum KL-6 level reflected pulmonary functional reserve in PM/DM patients with ILD. Ihn et al.¹⁴ reported that serum SP-D level was also significantly higher in PM/DM

patients with ILD than in PM/DM patients without ILD and the serum SP-D level was inversely correlated with percent vital capacity and percent diffusing capacity of the lungs for carbon monoxide.

Serum ferritin and interleukin-18. Gono et al reported that the serum ferritin level was elevated in anti-MDA5-positive clinically ADM (CADM) or DM patients¹⁵ and correlated with severity (A-aDO₂ and P/F ratio),¹⁵ prognosis,¹⁵ and disease activity of ILD in anti-MDA5-positive CADM or DM patients. In addition, serum interleukin-18 level was significantly correlated with response to therapy and prognosis of ILD in those patients.¹⁶ These findings imply that macrophage activation plays an important role in the pathophysiology of ILD in anti-MDA5-positive patients.

Autoantibodies Associated with ILD in IIM

Anti-ARS antibodies. Anti-ARS antibodies are seen in 25%–42% of all myositis patients^{6,7} and are also detected in patients with IIM or idiopathic interstitial pneumonia (IIP).¹⁷ ARS is essential when messenger RNA is translated to amino acids. The definition of anti-ARS antibodies includes not only their binding ability to ARS but also their blocking ability against the function of ARS.^{18–21} There have been reports of anti-Jo-1,¹⁸ anti-PL-7,¹⁹ anti-PL-12,²⁰ anti-EJ,²¹ anti-OJ,²¹ and anti-KS antibodies, which correspond to histidyl-, threonyl-, alanyl-, glycyl-, isoleucyl-, and asparaginyl-tRNA synthetases, respectively. Love et al.⁹ described five common symptoms, namely ILD, Raynaud's phenomenon, polyarthritides, high fever, and mechanic's hand, seen in anti-ARS-positive IIM patients and named them as anti-synthetase syndrome.

Anti-ARS antibodies may have stronger connections with ILD than with myopathy. A significant association of anti-ARS antibodies with ILD-preceding IIM patients has been reported (Fig. 1).²² Moreover, anti-ARS antibodies have been found in ILD patients without myopathy.^{17,22} Watanabe et al.²³ examined the histopathology of lungs sampled from eight anti-ARS-positive ILD-alone patients. Three patients showed cellular nonspecific interstitial pneumonia, three patients showed fibrous nonspecific interstitial pneumonia, and two patients showed usual interstitial pneumonia with cellular infiltration.²³ They also reported that chest high-resolution computed tomography (HRCT) revealed traction bronchiectasis, ground-glass opacity, lower reticulation, and subpleural sparing (Fig. 2), while honeycombing was not observed.²³ Additionally, shrinking lung is also a common finding of chest X-ray in anti-ARS-positive ILD patients.

ILD complicated by anti-ARS-positivity responds to immunosuppressive therapy but tends to show a recurrent clinical course. ILD in anti-ARS-positive patients showed a more favorable response to glucocorticoid therapy than in anti-ARS-negative patients,²² and a recurrent course of ILD was significantly more frequent in the anti-ARS-positive patients than in the anti-ARS-negative patients.²² These results imply that anti-ARS antibodies can be markers for clinical course prediction of ILD complicated with IIM. Indication of immunosuppressants, such as oral tacrolimus and intravenous cyclophosphamide, should be considered in patients with recurrent ILD complicated with IIM.

Hamaguchi et al.²⁴ investigated the difference in clinical features among patients positive for each kind of anti-ARS antibodies. ILD-alone cases were frequent in patients with anti-PL-12, anti-OJ, and anti-KS, while myopathy and rash were frequent in patients with anti-Jo-1, anti-PL-7, and anti-EJ. Polyarthritis is more strongly associated with anti-Jo-1 than with non-Jo-1 anti-ARS antibodies.^{24,25} Aggarwal et al.²⁵ reported that five-year survival was lower in patients with non-Jo-1 anti-ARS antibodies than in patients with anti-Jo-1 antibodies.

Recently, we established a new ELISA system (MESA-CUP™ Anti-ARS Test; MBL Co., Ltd.) that covers anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-KS antibodies simultaneously,¹⁷ and it is used daily in Japan. To diagnose IIM or idiopathic interstitial pneumonia, its sensitivity is 22.7% (95/418), and its specificity is 97.7% (299/306), using a cut-off level of 25 U/mL. The limitation of the system is that it cannot identify the kind of anti-ARS antibodies or anti-OJ.

Anti-MDA5 antibodies. Sontheimer²⁶ enlarged the category of ADM and referred the entity of CADM that includes hypomyopathic DM with typical rashes and subclinical myopathy. The study did not mention patients with rapidly progressive and fatal ILD and required a two-year observation with no evident myopathy to diagnose CADM. However, several cases of CADM complicated with devastating ILD have been reported from Asia and also from the USA²⁷ and Europe.²⁸ Those patients were refractory to immunosuppressive therapy leading to a fatal clinical course, and histopathology

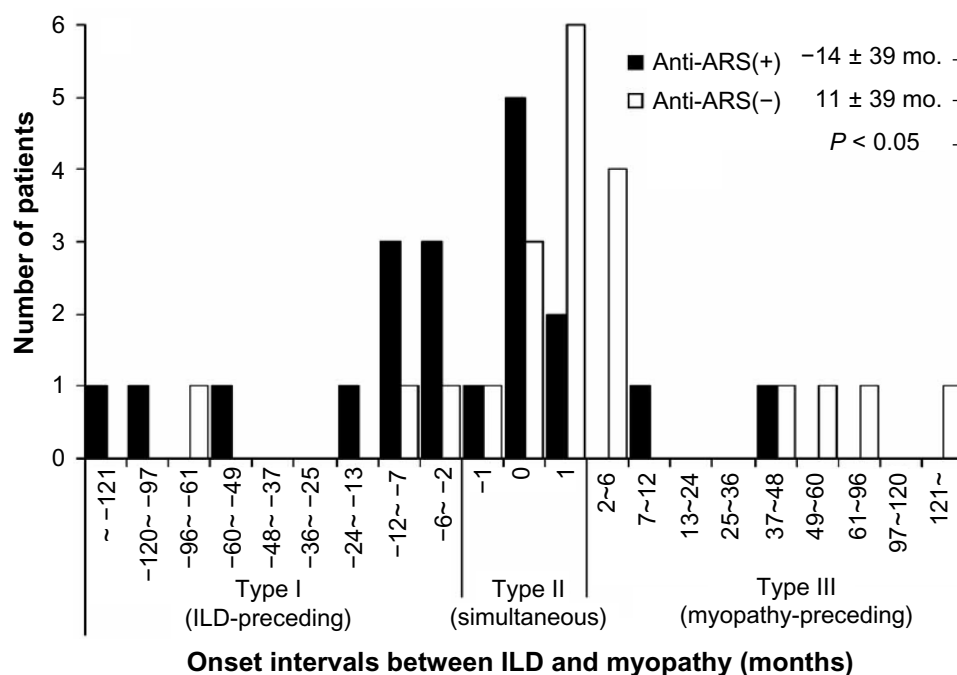


Figure 1. Onset intervals between ILD and myopathy in anti-ARS-positive and anti-ARS-negative patients.

Notes: Positive numbers indicate myopathy preceded ILD. Negative numbers indicate ILD preceded myopathy. The two symptoms are regarded as simultaneous if the interval is shorter than a month. Values in the upper-right corner are mean ± SD of the onset intervals.²²

Abbreviations: ARS, aminoacyl-tRNA synthetase; ILD, interstitial lung disease.

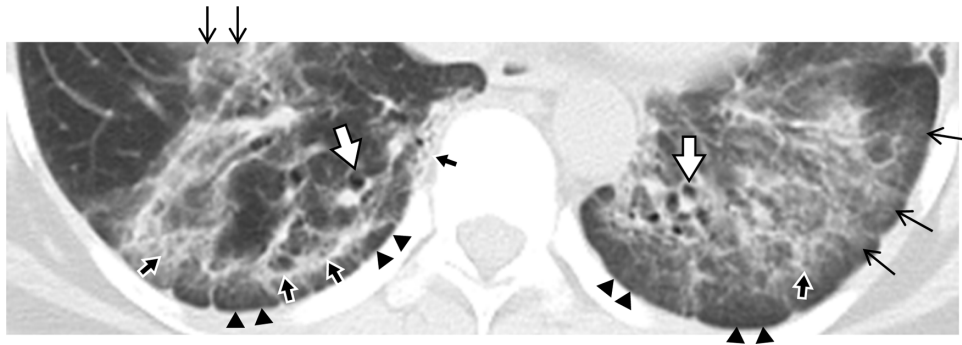


Figure 2. Chest HRCT image of an anti-ARS-positive patient.

Notes: Characteristic findings in anti-ARS-positive patients reported by Watanabe et al.²³ are indicated in a chest HRCT image of an anti-PL-7-positive patient treated by the author of this review. Triangles: subpleural sparing; small thick arrows: lower reticulation; large white arrows: traction bronchiectasis; and large thin arrows: ground-glass attenuation. Note that honeycombing is not observed.

Abbreviations: ARS, aminoacyl-tRNA synthetase; HRCT, high-resolution computed tomography; ILD, interstitial lung disease.

of the autopsied lungs showed diffuse alveolar damage. In 2005, Sato et al found anti-140 kDa antibodies in Japanese CADM patients,²⁹ and finally, MDA5 was identified as its target antigen.¹⁰

Anti-MDA5 antibodies are detected in CADM or DM patients.^{10,15,27,28,30} ILD is seen in 50%–100% of the anti-MDA5-positive CADM or DM patients.^{10,27,28,30} Tanizawa et al.³¹ reported that the findings of chest HRCT were dominated by (i) lower consolidation or ground-glass attenuation pattern and (ii) a random ground-glass attenuation pattern (Fig. 3). Mortality ranged from 36% to 46% in anti-MDA5-positive CADM or DM patients.^{10,15} If an anti-MDA5-positive patient shows even slowly progressive ILD, the most intensive immunosuppressive regimen should be considered to prevent ILD from advancing to a devastating status. Importantly, Teruya et al.³² reported that an anti-MDA5-positive ADM patient with rapidly progressive ILD was successfully treated with polymyxin-B direct hemoperfusion.

The titer of anti-MDA5 antibodies reflects the severity of ILD and skin ulcerations.³⁰ Cao et al.³⁰ reported that the titer

of anti-MDA5 antibodies reflected the HRCT score of lung lesions, and the titer was decreased after treatment.

Anti-U1-RNP antibodies. Anti-U1-RNP antibodies are found in major MAA associated with OS or mixed connective tissue disease and are associated with both myopathy and ILD.³³ The frequency ranges from 6% to 10% in all myositis.^{7,8} In general, ILD progresses chronically in anti-U1-RNP-positive patients. Glucocorticoids are effective in treating ILD in anti-U1-RNP-positive patients.³⁴

Anti-PM/Scl antibodies. The prognosis of ILD in anti-PM/Scl-positive patients cannot be determined currently because of the limited number of studies published. However, Muro et al.³⁵ reported that 4 of the 11 patients positive for anti-PM/Scl antibodies (two DM, one CADM, and one UCTD) had ILD. All of them required immunosuppressive therapy, although they did not show fatal outcomes.

Anti-Ku antibodies. The clinical course of ILD in anti-Ku-positive patients is also uncertain because the number of reports is limited. Rigolet et al.³⁶ reported that 11 of the 30

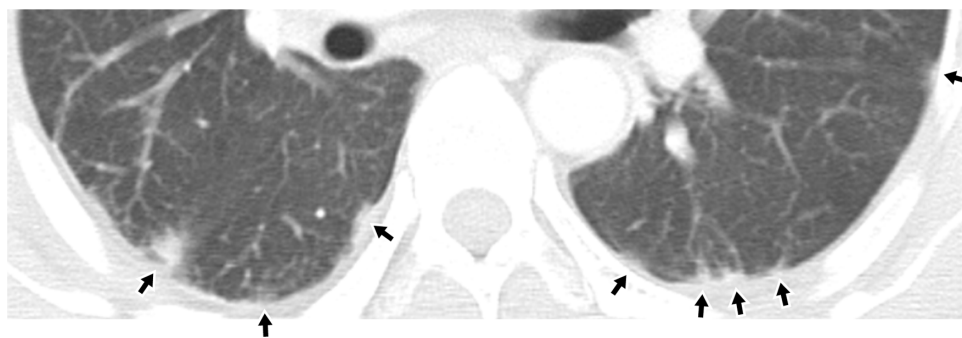


Figure 3. Chest HRCT image of an anti-MDA5-positive patient.

Notes: Random GGA patterns, reported by Tanizawa et al.³¹ are characteristic findings in anti-MDA5-positive patients and are indicated by arrows in a chest HRCT image of an anti-MDA5-positive patient treated by the author of this review.

Abbreviations: GGA, ground-glass attenuation; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MDA5, melanoma differentiation-associated protein 5.



anti-Ku-positive patients (mostly with IIM) had ILD. Eight of the 11 anti-Ku-positive patients with ILD received immunosuppressive therapy; however, their ILD was resistant to the therapy in six of the eight patients.

Application of Biomarkers and Autoantibodies to Treatments

According to the profiles of autoantibodies, ILD complicated with IIM can be divided into three groups: high-, moderate-, and low-risk groups.

High-risk group: anti-MDA5 antibodies. *Decisions for treatment.* In the patients with anti-MDA5 antibodies, treatment should begin before respiratory symptoms or impaired pulmonary function develops. When an anti-MDA5-positive patient shows characteristic chest HRCT findings and elevated biomarkers, such as serum LDH, KL-6, SP-D, and ferritin, the most aggressive immunosuppressive treatments should commence.

Follow-up. Symptoms, oxygenation status, image findings, serum LDH, KL-6, and SP-D will be measures of therapeutic effects. Serum ferritin, interleukin-18, and the titer of anti-MDA5 antibodies may reflect the activity of ILD in anti-MDA5-positive patients.

Moderate-risk group: anti-ARS, anti-U1-RNP, anti-PM/Scl, and anti-Ku antibodies. *Decisions for treatment.* Respiratory symptoms, speed of reduction in pulmonary function, and speed of expansion of chest HRCT findings should be taken into consideration to determine when to start immunosuppressive treatments.

Follow-up. Symptoms, pulmonary function, image findings, and universal activity markers of ILD (serum LDH, KL-6, and SP-D) are helpful to evaluate the potential outcomes of treatment. Anti-ARS-positive patients occasionally show recurrent ILD; therefore, careful attention is needed to detect any disease recurrence. Immunosuppressants should be considered in patients with recurrent ILD complicated with IIM.

Low-risk group: anti-Mi-2, anti-SRP, and anti-TIF1- γ/α antibodies. *Decisions for treatment.* Treatment should follow the same course as the moderate-risk group. However, because ILD is less common in patients with anti-Mi-2,³⁷ anti-SRP,³⁸ or anti-TIF1- γ/α antibodies,³⁹ careful consideration is needed before treating ILD in these patients. Possible overlap with other conditions including infectious or drug-induced pneumonia should be examined.

Conclusion

Serum LDH, KL-6, and SP-D reflect lung damage and are the activity markers of ILD complicated with IIM. Anti-ARS and anti-MDA5 antibodies are associated with ILD, while anti-Mi-2, SRP, and TIF1- γ/α antibodies are less so. Anti-MDA5 antibodies are associated with rapidly progressive ILD, while anti-ARS antibodies are not associated with rapidly progressive ILD but with a recurrent course of ILD. DM or CADM patients with anti-MDA5 and characteristic chest HRCT

findings are highly likely to have devastating ILD and require aggressive treatment.

Author Contributions

Conceived the concepts: HY. Analyzed the data: HY. Agree with manuscript results and conclusions: HY. Developed the structure and arguments for the paper: HY. Made critical revisions: HY. The author reviewed and approved of the final manuscript.

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