Journal of
Pulmonary & Respiratory Medicine

Liao et al., J Pulm Respir Med 2016, 6:6
DOI: 10.4172/2161-105X.1000383

Review Article OMICS International

Serological Biomarkers of Dermatomyositis – Associated Interstitial Lung Disease

Xining Liao[1], Yuan Liu[2], Yuechi Sun[2], Shiju Chen[2] and Guixiu Shi[2*]

[1]*Medical College, Xiamen University, Xiamen, Fujian, China*
[2]*Department of Rheumatology and Clinical Immunology, The First Affiliated Hospital of Xiamen University, No. 55, Zhenhai Road, Xiamen, China*

Abstract

Dermatomyositis (DM) is a subset of idiopathic inflammatory myopathies (IIM) which is characterized by chronic inflammation of skin and muscle weakness, and often involving other organs, such as skin, heart, gastrointestinal tract, pulmonary, and joints. Interstitial lung disease (ILD) is the most common internal organ manifestation that affects the prognosis of DM patients. The mortality is very high in DM-ILD patients especially in those with rapid ILD due to the lack of effective treatment. An early diagnosis of ILD in DM patients is critical important. In recent years, many studies focused on detecting serological biomarkers that can be used in prediction and evaluation of DM-ILD. Here we reviewed recent studies about serological biomarkers of DM-ILD. An overview of those biomarkers may help us have a better management of DM-ILD and may give us a better understanding about the pathogenesis of DM-ILD.

Keywords: Dermatomyositis; Interstitial lung disease; Biomarkers

Introduction

Dermatomyositis (DM) is a subset of idiopathic inflammatory myopathies (IIM) which is characterized by chronic inflammation of skin and muscle weakness, and often involving other organs, such as skin, heart, gastrointestinal tract, pulmonary, and joints [1-5]. The subtypes of DM include classical DM, which has muscle manifestations as well as a variety of cutaneous manifestations; another subset of DM is called clinically amyopathic dermatomyositis (CADM), referring to the typical clinical manifestations of dermatomyositis skin and few have the clinical manifestations of muscle weakness [6,7].

Interstitial lung disease (ILD) is the most common internal organ manifestation that affects the prognosis of DM patients [8]. It has been estimated that about 35% to 40% of patients with DM can incur interstitial lung disease (ILD) [4,9]. In the recent researches, the prevalence of ILD in myositis (include PM and DM) has reached close to 50%, ranging from 21% to 78% [8,10-16]. There are two different subtypes of ILD in DM *viz.,* chronic/subacute interstitial lung disease, and rapid progressive interstitial lung disease (RP-ILD) [8,10]. RP-ILD is critical important in the clinical management of DM patients since the mortality is very high and prognosis is very poor [8], with a 6-month survival rate of 40.8% to 45.0% [14,17]. Certain studies report that CADM patients, particularly in those Japanese descent, often suffer rapidly progressive interstitial lung disease [7]. Compared with classic DM with ILD, CADM-associated ILD often enjoys a worse prognosis [18-21].

The pathogenesis of ILD is not completely clear yet and lack of effective treatment. An early diagnosis of ILD, especially RP-ILD is quite important for the management of DM-ILD patients. Serological biomarkers are widely used in diagnosis of many kinds of diseases. In recent years, many researches focused on screening new biomarker specific for DM-ILD found several serological biomarkers might be used in clinical management of DM-ILD patients. Study of these new biomarkers can help us know more about the pathogenesis, pathological process and prognosis of the disease. In this article, we reviewed recent reports of biomarkers associated with ILD in DM patients.

Autoantibodies

Anti-aminoacyl-transfer RNA synthetase antibodies

There is evidence that DM is an autoimmune disease. Approximately 50% to 70% of patients have been detected with circulating myositis-specific autoantibodies (MSAs). The primary component of MSAs is anti-synthetase antibodies. Numerous clinical cases suggest that in patients with anti-aminoacyl-transfer RNA synthetase antibodies (anti-ARS Abs), known as anti-synthetase antibodies, more than 63% to 75% will appear ILD [22,23], yet, the relationship between anti-ARS Abs and activity of dermatomyositis or ILD is disputable [24].

Thus far, there are eight different anti-ARS antibodies have been identified: anti-Jo-1 (histidyl), anti-PL-7 (threonyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginyl), anti-Zo (phenylalanyl), and anti-tyrosyl-tRNA synthetase antibodies [25-32]. There are some differences in detail clinical manifestations among patients with different anti-ARS antibodies. Anti-Jo-1 antibody, some studies have shown that patients with this antibody (a major type of anti-ARS antibodies) positivity combined ILD, meanwhile with high prevalence of myositis, and its prognosis is better than others [6,33]. However, anti-OJ, anti-PL-12, and anti-KS are more likely associations with ILD than myositis, particularly anti-KS [31]. Anti-PL-7 may be associated with DM-scleroderma overlap syndrome as well as with ILD, especially in Japanese patients [34]. It is still uncertain whether these autoantibodies play a role in the pathophysiologic mechanisms of disease.

In a retrospective study, Yoshifuji et al. [35] has shown that patients with ILD had a better response to the initial stage of cortisol therapy, but the recurrence rate was significantly increased compared with those who were negative for the anti-ARS antibodies. In addition, anti-ARS antibodies frequently appear in sera laboratory testing from chronic/subacute ILD patients and these patients tend to have recurrent

***Corresponding author**: Guixiu Shi, Department of Rheumatology and Clinical Immunology, The First Affiliated Hospital, Xiamen University, No. 55, Zhenhai Road, Xiamen-361003, China, Tel: +86 13600932661; Fax: +86 5922137769; E-mail: guixiu.shi@gmail.com

Received October 27, 2016; **Accepted** December 02, 2016; **Published** December 05, 2016

Citation: Liao X, Liu Y, Sun Y, Chen S, Shi G (2016) Serological Biomarkers of Dermatomyositis – Associated Interstitial Lung Disease. J Pulm Respir Med 6: 383. doi: 10.4172/2161-105X.1000383

illness. Early anti-ARS antibody screening can be used to predict late-onset DM, if the patient had pulmonary involvement as the initial manifestation of the disease, and can predict the progression of ILD in patients with dermatomyositis. However, certain literatures report that although these antibodies have myositis-specific, they appear less frequently in DM patients [36], and the role of these antibodies in the pathogenesis of DM patients combined with ILD is yet to be further studied.

Approximately 20% to 30% of the DM patients may be detected to have anti-Mi-2, which interacts with Mi-2, a nuclear helicase protein. It is the primary DM-specific MSA to be identified. The data shows that the DM patients with anti-Mi-2 positive are more likely to have lower morbidity of ILD and malignancy, as well as sensitivity to steroids [36].

Anti-CADM-140/MDA5 antibody

Recently, some Japanese literature reveals, the discovery of a novel antibody in CADM patients, the anti-MDA-5/CADM-140 antibody [37]. Since the Japanese scientists found that this antibody directly interacts with an RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA-5), this antibody is also referred to as anti-MDA5 antibody [38]. This RNA helicase defense the virus infection in the innate immune. CADM patients who have this antibody appear are associated with an obviously higher rate of rapidly progressive ILD, and a severe clinical course [18-21,39]. Serological laboratory testing of approximately a quarter of patients with DM or a half of patients with CADM may presence this antibody, whereas it cannot be detected in other disease [18,39-42]. Currently, the presence of this antibody has been detected in an increasing number of races, including Caucasian, Israel, and so on [42,43].

Chronic and subacute ILD patients often represent anti-synthetase-positive, whereas acute ILD patients are often associated with anti-MDA5 antibody. In the presence of anti-synthetase antibodies, approximately 30% to 50% of patients initially showed lung lesions [22,35,44].

There are also some DM specific MSA, but they need further analysis. These antibodies include anti-SAE, a novel autoantibody directed against small ubiquitin-like modifier activating enzyme, only in a UK cohort of DM patients. Betteridge et al. [45] have also found that the DM patients with this autoantibody be likely to have a lower prevalence of ILD.

There are other autoantibodies, which are not only present in myositis, but also occur in other connective tissue diseases, particularly in patients with systemic scleroderma and overlap syndrome. Anti-SS-A/Ro antibody, coexistence of anti-SS-A and anti-Jo-1 antibody, recently certain studies finding that may be a biomarker in DM-ILD patients. Compared with the anti-SS-A/Ro antibody-negative patients, anti-SS-A/Ro antibody present in anti-synthetase syndrome patients may be accompanied seem more severe ILD, and a poor response immunosuppressive treatment. Meanwhile, compared with classical dermatomyositis without anti-synthetase syndrome, the patients with anti-synthetase syndrome showed elevate frequency of the presence of ILD, and anti-Ro/SSA antibodies [46,47]. Muro et al. [48] has report that they found a novel autoantibody. In their study, 126 DM patients, of whom 3 patients had anti-PM/Scl antibodies, and the 3 patients were all complicated with ILD. The clinical manifestations of ILD for these three patients did not have a fatal outcome [48]. Principal autoantibodies associated with ILD in DM patients are summarized in Table 1.

However, so far, there is no conclusive evidence shown that these autoantibodies are also associated with other phenotype of ILD, such as nonspecific interstitial pneumonitis (NSIP).

Lung Epithelium-Specific Biomarkers

Although HRCT examination of pulmonary is the most sensitive method for detection and prediction of ILD activation as of now. However, frequent exposure to CT high-radiation is harmful to the human body. Therefore, it is important to detect the biomarkers that may accompanying with inflammatory activation of lung.

Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are recently identified biomarkers associated with DM-ILD. They are both secreted by type II alveolar epithelial cells. Some studies have shown that they are significantly elevated in the serum of patients with DM-ILD, and they are positively correlated with the prognosis of the disease [49-52]. They can be used as biomarkers in the serum of DM-ILD patients. Ohnishi [50], also suggested that KL-6 might be more sensitive than SP-D in the detection of DM-ILD patients [53,54]. Some studies have indicated that in a more common type of disease in ILD, idiopathic pulmonary fibrosis (IPF) also known as usual interstitial pneumonia (UIP), the level of KL-6 and SP-D is also higher than the normal group, and the increased levels predictors of worse survival [55-58]. However, so far, there is no conclusive evidence shown that KL-6 and SP-D are also associated with other phenotype of idiopathic interstitial pneumonia (IIP), such as nonspecific interstitial pneumonitis (NSIP). Clinical significance of lung epithelium specific biomarkers is summarized in Table 2.

Cytokines

In a number of studies on juvenile dermatomyositis (JDM), accompanied with rapidly progressive interstitial lung disease (RP-ILD) group and chronic ILD (C-ILD) group, the serum B cell activating

Autoantibody	Prevalence in DM patients with ILD (%)	Prevalence in DM patients without ILD (%)	Clinical significance	References
Anti-ARS autoantibodies	>63% to 70.4%	3%	Associated with chronic or recurrent ILD	[22,47]
Anti-Jo-1 autoantibody	13.6%	24%	Prevalence of ILD is lower in anti-Jo-1 positive DM patients than other anti-ARS autoantibodies-positive DM patients.	[6,31,33]
Anti-Mi-2 autoantibody	undetermined	undetermined	Patients with positive anti-Mi-2 often have lower morbidity caused by ILD and sensitivity to steroids.	[36]
Anti-MDA5 autoantibody	92% to 100%	63.3%	Specific to CADM; often associated with rapidly progressive ILD, severe skin manifestations; The levels of this antibody would be helpful in predicting the course of ILD and facilitating better therapeutic targeting.	[18,20,39-42]
Anti-SAE autoantibody	Maybe Lower	undetermined	More research is needed on this antibody.	[32]
Anti-PM/Scl autoantibodies	undetermined	undetermined	Patients with this antibody often have a good response of oral prednisolone and immune suppressive agent therapy.	[48]

Table 1: Principal autoantibodies associated with ILD in DM patients.

factor (BAFF) and a proliferation-inducing ligand (APRIL) titers were significantly higher, while the C-ILD group was significantly higher than healthy controls. They also indicated that the levels of BAFF and APRIL were associated with serum Krebs von den Lungen-6 (KL-6) and interleukin 18 (IL-18) in patients with ILD, and the patients have high titer anti-MDA5 (>200 U), also had higher levels of BAFF and APRIL [59]. However, in the adult DM-ILD, whether there is a correlationship between titer of these cytokines and RP-ILD, there is no report so far.

Cathepsin B (CB) is a cysteine protease, which belongs to the family of the papaya protease, mostly located in lysosomes [60]. The function of this protease is mainly involved in the turnover of proteins and play a various roles in maintaining the normal metabolism of cells. Recent year, Zhang et al. [60] have showed that in cytoplasm of the lung tissues from PM/DM patients, the number of CB-positive cells was obviously higher than healthy controls. They also suggest that CB through activate the TNF-a signaling mediates pulmonary cell apoptosis.

Some research suggests that in the serological detection of DM patients, IL-18 was significantly elevated, especially with disease activity and ILD presence in DM. At the same time, Gono et al. [61] also found in some patients with the activity of acute ILD in DM, their serum ferritin and IL-18 both higher than others.

There are many cytokines and chemokines could take part in the whole disease status, including dermatitis and ILD, in DM [62]. The levels of IL-6, IL-8, IL-10, TNF-a and IP-10 (IFN-g-inducible 10 kDa protein) were significantly elevated in the DM/PM/CADM patients with ILD [62-64]. And, the most significantly cytokine was TNF-a [62]. In addition, the titer of serum IL-8 between chronic ILD (anti-ARS-ILD) and RP-ILD (anti-MDA5-ILD) were different, the levels were significantly higher in RP-ILD than chronic ILD [62]. Thus, the levels of IL-8 can be a useful predictor for fatal outcomes due to ILD with PM/DM. While some studies have reported that IL-6, IL-8, and IL-10 may be significant contributors to up-regulation of the level of ferritin in PM/DM, thus induce RP-ILD, there are some reports found IFN-g-inducible chemokines C-X-C motif ligand 9 (CXCL9) and CXCL10 were associated with anti-Jo-1 antibody-associated ILD [64,65]. In these cytokines, IL-6 and IL-8 also associated with IPF, and high concentrations may associate with worse survival [66]. Cytokines involved in DM-ILD are summarized in Table 3.

Other serological biomarkers

Serum ferritin is another novel biomarker detected in DM-ILD patients. They may be found mainly in patients with acute or subacute progressive ILD, particularly in CADM patients [41,67-69]. In addition, the studies have shown that the level of serum ferritin was obviously higher in ILD patients with anti-MDA5-positive [68,69].

Some serum protein biomarker, such as the general inflammatory markers C-reactive protein (CRP) have been reported that may associated with anti-Jo-1 antibody-associated ILD [64].

Limited articles reported BALF cells profiles. There were two different studies suggested that patients with ILD had a poor outcome when the initial BALF showed neutrophilic alveolitis [8,10]. However, these markers weather have universality in the serological detection of patients with dermatomyositis-associated ILD, are in need of more researches.

There are some new biomarkers which have been reported or accepted so far associated with DM, include anti-MJ/nuclear matrix protein 2 (NXP-2) and anti-small ubiquitin-like modifier-1 (SUMO-1) activating enzyme (SAE), but whether they also play a role in the pathogenesis of DM patients with ILD, also needs more research. Other serological biomarkers of DM-ILD are summarized in Table 4.

Perspectives

ILD is the most frequent complication of DM patients [23,70], and the morbidity and mortality will be greatly increased in DM-ILD

Lung epithelium-specific biomarkers	Serum level in DM patients with ILD	Serum level in DM patients without ILD	Clinical significance	References
KL-6	Median 995 (range 533-2318) U/mL	Median 322 (range 132-1225) U/mL	May be the best serum marker for ILD; Reflected the extent and severity of ILD; The level of KL-6 >1000 U/mL may indicate poor prognosis; The changes in serum KL-6 levels correlated significantly with changes in pulmonary function tests. The level of KL-6 also associated with UIP.	[50,51,53]
SP-D	118.7 ng/ml ± 220.2 ng/ml	38.7 ng/ml ± 21.0 ng/ml	The serum SP-D level in PM/DM patients with ILD was significantly elevated compared with those without ILD, it can reflect the severity of ILD in patients with PM/DM. The level of SP-D also associated with UIP.	[49]

Table 2: Principal lung epithelium-specific biomarkers associated with ILD in DM patients.

Cytokines	Clinical significance	References
BAFF	Serum BAFF titers were significantly higher in the juvenile dermatomyositis (JDM) patients with RP-ILD versus those with C-ILD and healthy controls.	[55]
APRIL	Serum APRIL titers were significantly higher in the juvenile dermatomyositis (JDM) patients with RP-ILD versus those with C-ILD and healthy controls.	[55]
CB	The cytokine may act through activate the TNF-a signaling and mediate pulmonary cell apoptosis.	[56]
IL-6	IL-6 was associated with global disease activity in PM, DM and CADM; The cytokine level was high, especially in ILD with PM/DM; IL-6 is significant factors that contribute to serum ferritin levels. The level of IL-6 also associated with UIP.	[58,61]
IL-8	Serum IL-8 levels may contribute to the differences in pathophysiology between chronic ILD (anti-ARS-ILD) and RP-ILD (anti-MDA5-ILD); A useful predictor for fatal outcomes due to ILD with PM/DM. The level of IL-8 also associated with UIP.	[58,61]
IL-10	IL-10 was associated with global disease activity in PM, DM and CADM; a significant factor that contribute to serum ferritin levels.	[58,61]
IL-18	IL-18 was significantly elevated, especially associated with disease activity and ILD presence in DM	[57]
IP-10	IP-10 was associated with global disease activity in PM, DM and CADM; The cytokine level was high, especially in ILD with PM/DM.	[58]
TNF-α,	In IL-6, IL-8, IL-10 and TNF-a, TNF-αmay be the cytokine that was most significantly associated with ILD in PM/DM/CADM.	[58]
CXCL9	The level was associated with anti-Jo-1 antibody-associated ILD.	[60]
CXCL10	The level was associated with anti-Jo-1 antibody-associated ILD.	[60]

Table 3: Principal cytokines associated with ILD in DM patients.

Biomarkers	Clinical significance	References
Ferritin	Serum ferritin can be useful as a predictor of the occurrence of acute or subacute progressive ILD (A/SIP) and correlates with the prognosis of A/SIP in DM; The cumulative survival rate was significantly lower when the ferritin levels > or =1500 ng/ml.	[62]
CRP	The level is associated with anti-Jo-1 antibody-associated ILD.	[60]
BALF cells profiles	Two different studies suggested that patients with ILD had a poor outcome when the initial BALF showed neutrophilic alveolitis.	[60]

Table 4: Other biomarkers associated with ILD in DM patients.

patients [12,23]. Fujisawa et al. [71] indicate that although another idiopathic inflammatory myopathies (IIM), known as polymyositis (PM), appeared to have a similar frequency of ILD as DM patients, however, the mortality of PM-ILD is lower, and more sensitive to drug treatment, and the prognosis is better than DM-ILD [71-73]. Early diagnosis of ILD is critical important for the management of DM patients since there is still lack of effective treatment of DM-ILD. Serological biomarkers are the most frequent method used in diseased diagnosis. Besides other testing methods include high-resolution CT (HRCT) scanning and pulmonary function tests for DM-ILD patients, serological biomarkers are also needed.

Studies in recent years have found several serological biomarkers associated with DM-ILD. Autoantibodies including anti-aminoacyl-transfer RNA synthetase antibodies (except anti-Jo-1) and anti-CADM-140 may be associated with high prevalence of ILD in DM patients. Lung epithelium-specific biomarkers including Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are newly detected biomarkers that have great potential in clinical management of DM-ILD. Cytokines including B cell activating factor (BAFF), a proliferation-inducing ligand (APRIL), cathepsin B, IL-6, IL-8, IL-10, IL-18, IP-10, TNF-α, CXCL9 and CXCL10 are increased in DM-ILD patients and may be involved in the pathogenesis of DM-ILD. Other serological biomarkers such as CRP and ferritin were also increased in DM-ILD patients.

Despite the growing number of biomarkers have been detected, there are still some limitations in these studies. First of all, studies on these biomarkers are mostly retrospective analyses, and due to the low incidence of DM-ILD, the number of patients in these reports was always relatively small. We need further prospective studies in larger number of DM-ILD patients, such as anti-ARS autoantibodies, anti-Jo-1 autoantibody, anti-Mi-2 autoantibody, anti-SAE autoantibody, anti-PM/Scl autoantibodies. Secondly, although some biomarkers have been confirmed by a large number of experiments, even has been used for clinical diagnosis, like anti-MDA5 autoantibody, KL-6, IL-6 and IL-8, we still know very little about the function of these biomarkers so far, more researches on their function may help us know the pathogenesis of DM-ILD. There are some newly detected biomarkers associated with autoimmune associated ILD, for instance, matrix metallo-proteinase-7 (MMP-7) is a potential biomarkers for rheumatoid arthritis-interstitial lung disease (RA-ILD). Whether there is clinical significance of these biomarkers in the serum of DM-ILD patients, may be a new research direction in the future. As more and more new biomarkers are detected, we will know more about the pathogenesis, pathological process, prognosis of the DM-ILD, and may provide us new treatment target for DM-ILD.

Conclusion

A large number of novel biomarkers have been found associated with DM-ILD, some may be used for diagnosis, evaluation of disease severity, progression and responsiveness to treatments. Clinical significance of biomarkers in DM-ILD patients including anti-MDA5 autoantibody, KL-6, SP-D, IL-6 and IL-8 have been proved by a large number of experiments, and KL-6 have been used in clinical management of DM-ILD as well as other type of ILD. Other biomarkers, like anti-ARS autoantibodies, anti-Jo-1 autoantibody, anti-Mi-2 autoantibody, anti-SAE autoantibody, anti-PM/Scl autoantibodies, BAFF, APRIL, CB, IL-10, IL-18, IP-10, TNF-α, CXCL9, CXCL10, ferritin, CRP, BALF cells profiles and MMP-7, may be used as potential serological biomarker in DM-ILD management, however, their clinical significance still need to be further evaluated in prospective studies with larger number of DM-ILD patients. Other kind of biomarkers including KL-6, SP-D, IL-6 and IL-8 have been proved not only associated with DM-ILD, but also with IPF.

Acknowledgments

The work was partially supported by NSFC (Natural Science Foundation of China) grant 81273285 and Xiamen Science and Technology Bureau Project no.3502Z20144005 to Dr. Guixiu Shi and NSFC (Natural Science Foundation of China) grant 81501407 to Dr. Yuan Liu.

Reference

1. Dalakas MC (1991) Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med 325: 1487-1498.
2. Dalakas MC, Hohlfeld R (2003) Polymyositis and dermatomyositis. Lancet 362: 971-982.
3. Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, et al. (2004) 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 200, Naarden, The Netherlands. Neuromuscul Disord 14: 337-345.
4. Marvi U, Chung L, Fiorentino DF (2012) Clinical presentation and evaluation of dermatomyositis. Indian J Dermatol 57: 375-381.
5. Findlay AR, Goyal NA, Mozaffar T (2015) An overview of polymyositis and dermatomyositis. Muscle Nerve 51: 638-656.
6. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD (2006) A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 54: 597-613.
7. Sato S, Kuwana M (2010) Clinically amyopathic dermatomyositis. Curr Opin Rheumatol 22: 639-643.
8. Marie I, Hachulla E, Chérin P, Dominique S, Hatron PY, et al. (2002) Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 47: 614-622.
9. Fathi M, Lundberg IE, Tornling G (2007) Pulmonary complications of polymyositis and dermatomyositis. Semin Respir Crit Care Med 28: 451-458.
10. Schnabel A, Reuter M, Biederer J, Richter C, Gross WL (2003) Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. Semin Arthritis Rheum 32: 273-284.
11. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G (2004) Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis 63: 297-301.
12. Kang EH, Lee EB, Shin KC, Im CH, Chung DH, et al. (2005) Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology (Oxford) 44: 1282-1286.
13. Won Huh J, Soon Kim D, Keun Lee C, Yoo B, Bum Seo J, et al. (2007) Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Respir Med 101: 1761-1769.
14. Ye S, Chen XX, Lu XY, Wu MF, Deng Y, et al. (2007) Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. Clin Rheumatol 26: 1647-1654.
15. Fathi M, Vikgren J, Boijsen M, Tylen U, Jorfeldt L, et al. (2008) Interstitial

lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. Arthritis Rheum 59: 677-685.

16. Chen IJ, Jan Wu YJ, Lin CW, Fan KW, Luo SF, et al. (2009) Interstitial lung disease in polymyositis and dermatomyositis. Clin Rheumatol 28: 639-646.

17. Mukae H, Ishimoto H, Sakamoto N, Hara S, Kakugawa T, et al. (2009) Clinical differences between interstitial lung disease associated with clinically amyopathic dermatomyositis and classic dermatomyositis. Chest 136: 1341-1347.

18. Kang EH, Nakashima R, Mimori T, Kim J, Lee YJ, et al. (2010) Myositis autoantibodies in Korean patients with inflammatory myositis: anti-140-kDa polypeptide antibody is primarily associated with rapidly progressive interstitial lung disease independent of clinically amyopathic dermatomyositis. BMC Musculoskelet Disord 11: 223.

19. Kobayashi I, Okura Y, Yamada M, Kawamura N, Kuwana M, et al. (2011) Anti-melanoma differentiation-associated gene 5 antibody is a diagnostic and predictive marker for interstitial lung diseases associated with juvenile dermatomyositis. J Pediatr 158: 675-677.

20. Cao H, Pan M, Kang Y, Xia Q, Li X, et al. (2012) Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. Arthritis Care Res (Hoboken) 64: 1602-1610.

21. Muro Y, Sugiura K, Hoshino K, Akiyama M (2012) Disappearance of anti-MDA-5 autoantibodies in clinically amyopathic DM/interstitial lung disease during disease remission. Rheumatology (Oxford) 51: 800-804.

22. Matsushita T, Hasegawa M, Fujimoto M, Hamaguchi Y, Komura K, et al. (2007) Clinical evaluation of anti-aminoacyl tRNA synthetase antibodies in Japanese patients with dermatomyositis. J Rheumatol 34: 1012-1018.

23. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK (2010) Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 138: 1464-1474.

24. Mimori T, Nakashima R, Hosono Y (2012) Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep 14: 264-274.

25. Nishikai M, Reichlin M (1980) Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. Arthritis Rheum 23: 881-888.

26. Mathews MB, Bernstein RM (1983) Myositis autoantibody inhibits histidyl-tRNA synthetase: a model for autoimmunity. Nature 304: 177-179.

27. Mathews MB, Reichlin M, Hughes GR, Bernstein RM (1984) Anti-threonyl-tRNA synthetase, a second myositis-related autoantibody. J Exp Med 160: 420-434.

28. Bunn CC, Bernstein RM, Mathews MB (1986) Autoantibodies against alanyl-tRNA synthetase and tRNAAla coexist and are associated with myositis. J Exp Med 163: 1281-1291.

29. Targoff IN, Trieu EP, Plotz PH, Miller FW (1992) Antibodies to glycyl-transfer RNA synthetase in patients with myositis and interstitial lung disease. Arthritis Rheum 35: 821-830.

30. Targoff IN, Trieu EP, Miller FW (1993) Reaction of anti-OJ autoantibodies with components of the multi-enzyme complex of aminoacyl-tRNA synthetases in addition to isoleucyl-tRNA synthetase. J Clin Invest 91: 2556-2564.

31. Hirakata M, Suwa A, Nagai S, Kron MA, Trieu EP, et al. (1999) Anti-KS: identification of autoantibodies to asparaginyl-transfer RNA synthetase associated with interstitial lung disease. J Immunol 162: 2315-2320.

32. Betteridge Z, Gunawardena H, North J, Slinn J, McHugh N (2007) Anti-synthetase syndrome: a new autoantibody to phenylalanyl transfer RNA synthetase (anti-Zo) associated with polymyositis and interstitial pneumonia. Rheumatology (Oxford) 46: 1005-1008.

33. Shen M, Gong Y, Zeng X, Zhang F, Tang F (2014) Interstitial lung disease as an initial manifestation of dermatomyositis. Zhonghua Yi Xue Za Zhi 94: 3402-3406.

34. Sato S, Kuwana M, Hirakata M (2007) Clinical characteristics of Japanese patients with anti-OJ (anti-isoleucyl-tRNA synthetase) autoantibodies. Rheumatology (Oxford) 46: 842-845.

35. Yoshifuji H, Fujii T, Kobayashi S, Imura Y, Fujita Y, et al. (2006) Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. Autoimmunity 39: 233-241.

36. Mammen AL (2010) Dermatomyositis and polymyositis: Clinical presentation, autoantibodies, and pathogenesis. Ann N Y Acad Sci 1184: 134-153.

37. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, et al. (2005) Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 52: 1571-1576.

38. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, et al. (2009) RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: Association with rapidly progressive interstitial lung disease. Arthritis Rheum 60: 2193-2200.

39. Hamaguchi Y, Kuwana M, Hoshino K, Hasegawa M, Kaji K, et al. (2011) Clinical correlations with dermatomyositis-specific autoantibodies in adult Japanese patients with dermatomyositis: a multicenter cross-sectional study. Arch Dermatol 147: 391-398.

40. Hoshino K, Muro Y, Sugiura K, Tomita Y, Nakashima R, et al. (2010) Anti-MDA5 and anti-TIF1-gamma antibodies have clinical significance for patients with dermatomyositis. Rheumatology (Oxford) 49: 1726-1733.

41. Nakashima R, Imura Y, Kobayashi S, Yukawa N, Yoshifuji H, et al. (2010) The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford) 49: 433-440.

42. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L (2011) The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. J Am Acad Dermatol 65: 25-34.

43. Gil B, Merav L, Pnina L, Chagai G (2016) Diagnosis and treatment of clinically amyopathic dermatomyositis (CADM): a case series and literature review. Clin Rheumatol 35: 2125-2130.

44. Koreeda Y, Higashimoto I, Yamamoto M, Takahashi M, Kaji K, et al. (2010) Clinical and pathological findings of interstitial lung disease patients with anti-aminoacyl-tRNA synthetase autoantibodies. Intern Med 49: 361-369.

45. Betteridge Z, Gunawardena H, North J, Slinn J, McHugh N (2007) Identification of a novel autoantibody directed against small ubiquitin-like modifier activating enzyme in dermatomyositis. Arthritis Rheum 56: 3132-3137.

46. La Corte R, Lo Mo Naco A, Locaputo A, Dolzani F, Trotta F (2006) In patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease. Autoimmunity 39: 249-253.

47. Váncsa A, Csípo I, Németh J, Dévényi K, Gergely L, et al. (2009) Characteristics of interstitial lung disease in SS-A positive/Jo-1 positive inflammatory myopathy patients. Rheumatol Int 29: 989-994.

48. Muro Y, Hosono Y, Sugiura K, Ogawa Y, Mimori T, et al. (2015) Anti-PM/Scl antibodies are found in Japanese patients with various systemic autoimmune conditions besides myositis and scleroderma. Arthritis Res Ther 17: 57.

49. Ihn H, Asano Y, Kubo M, Yamane K, Jinnin M, et al. (2002) Clinical significance of serum surfactant protein D (SP-D) in patients with polymyositis/dermatomyositis: correlation with interstitial lung disease. Rheumatology (Oxford) 41: 1268-1272.

50. Ohnishi H, Yokoyama A, Kondo K, Hamada H, Abe M, et al. (2002) Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. Am J Respir Crit Care Med 165: 378-381.

51. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M (2006) Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. J Intern Med 260: 429-434.

52. Kumanovics G, Minier T, Radics J, Palinkas L, Berki T, et al. (2008) Comprehensive investigation of novel serum markers of pulmonary fibrosis associated with systemic sclerosis and dermato/polymyositis. Clin Exp Rheumatol 26: 414-420.

53. Fathi M, Barbasso Helmers S, Lundberg IE (2012) KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis. J Intern Med 271: 589-597.

54. Arai S, Kurasawa K, Maezawa R, Owada T, Okada H, et al. (2013) Marked increase in serum KL-6 and surfactant protein D levels during the first 4 weeks after treatment predicts poor prognosis in patients with active interstitial pneumonia associated with polymyositis/dermatomyositis. Mod Rheumatol 23: 872-883.

55. Barlo NP, van Moorsel CH, Ruven HJ, Zanen P, van den Bosch JM, et al. (2009)

Surfactant protein-D predicts survival in patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 26: 155-161.

56. Kinder BW, Brown KK, McCormack FX, Ix JH, Kervitsky A, et al. (2009) Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. Chest 135: 1557-1563.

57. Ohshimo S, Ishikawa N, Horimasu Y, Hattori N, Hirohashi N, et al. (2014) Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. Respir Med 108: 1031-1039.

58. Yokoyama A, Kondo K, Nakajima M, Matsushima T, Takahashi T, et al. (2006) Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology 11: 164-168.

59. Kobayashi N, Kobayashi I, Mori M, Sato S, Iwata N, et al. (2015) Increased Serum B Cell Activating Factor and a Proliferation-inducing Ligand Are Associated with Interstitial Lung Disease in Patients with Juvenile Dermatomyositis. J Rheumatol 42: 2412-2418.

60. Zhang L, Fu XH, Yu Y, Shui RH, Li C, et al. (2015) Treatment with CA-074Me, a Cathepsin B inhibitor, reduces lung interstitial inflammation and fibrosis in a rat model of polymyositis. Lab Invest 95: 65-77.

61. Gono T, Sato S, Kawaguchi Y, Kuwana M, Hanaoka M, et al. (2012) Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology (Oxford) 51: 1563-1570.

62. Gono T, Kaneko H, Kawaguchi Y, Hanaoka M, Kataoka S, et al. (2014) Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology (Oxford) 53: 2196-2203.

63. Bilgic H, Ytterberg SR, Amin S, McNallan KT, Wilson JC, et al. (2009) Interleukin-6 and type I interferon-regulated genes and chemokines mark disease activity in dermatomyositis. Arthritis Rheum 60: 3436-346.

64. Richards TJ, Eggebeen A, Gibson K, Yousem S, Fuhrman C, et al. (2009) Characterization and peripheral blood biomarker assessment of anti-Jo-1 antibody-positive interstitial lung disease. Arthritis Rheum 60: 2183-2192.

65. Kawasumi H, Gono T (2014) IL-6, IL-8, and IL-10 are associated with hyperferritinemia in rapidly progressive interstitial lung disease with polymyositis/dermatomyositis. Biomed Res Int 2014: 815245.

66. Richards TJ, Kaminski N, Baribaud F, Flavin S, Brodmerkel C, et al. (2012) Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 185: 67-76.

67. Gono T, Kawaguchi Y, Hara M, Masuda I, Katsumata Y, et al. (2010) Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 49: 1354-1360.

68. Gono T, Kawaguchi Y, Ozeki E, Ota Y, Satoh T, et al. (2011) Serum ferritin correlates with activity of anti-MDA5 antibody-associated acute interstitial lung disease as a complication of dermatomyositis. Mod Rheumatol 21: 223-227.

69. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, et al. (2010) Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 49: 1713-1719.

70. Labirua A, Lundberg IE (2010) Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. Curr Opin Rheumatol 22: 633-638.

71. Fujisawa T, Suda T, Nakamura Y, Enomoto N, Ide K, et al. (2005) Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. J Rheumatol 32: 58-64.

72. Hayashi S, Tanaka M, Kobayashi H, Nakazono T, Satoh T, et al. (2008) High-resolution computed tomography characterization of interstitial lung diseases in polymyositis/dermatomyositis. J Rheumatol 35: 260-269.

73. Yamasaki Y, Yamada H, Ohkubo M, Yamasaki M, Azuma K, et al. (2011) Longterm survival and associated risk factors in patients with adult-onset idiopathic inflammatory myopathies and amyopathic dermatomyositis: experience in a single institute in Japan. J Rheumatol 38: 1636-1643.