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Comprehensive assessment of myositis-specific autoantibodies in polymyositis/dermatomyositis-associated interstitial lung disease

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ABSTRACT

Objectives: Myositis-specific autoantibodies (MSAs) are associated with clinical phenotypes in polymyositis/dermatomyositis (PM/DM). No study has investigated the clinical features based on comprehensive MSA assessment in PM/DM-associated interstitial lung disease (ILD). We aimed to determine the practical significance of MSAs in PM/DM-ILD.

Methods: Sixty consecutive PM/DM-ILD patients were retrospectively analysed. Serum MSAs were comprehensively measured using immunoprecipitation assay. Clinical features and prognosis were compared among MSA subgroups.

Results: Twenty-six (43.3%) PM/DM-ILD patients were anti-aminoacyl tRNA-synthetase antibody-positive (anti-ARS-positive), 15 (25.0%) were anti-melanoma differentiation-associated gene 5 antibody-positive (anti-MDA5-positive), 3 (5%) were anti-signal recognition particle antibody-positive, 1 (1.7%) was anti-transcriptional intermediary factor 1-gamma antibody-positive, and 15 (25%) were MSA-negative. There were significant differences in clinical features, including ILD form, serum ferritin and surfactant protein-D levels at ILD diagnosis, and high-resolution CT pattern among the anti-ARS-positive, anti-MDA5-positive and MSA-negative groups. The anti-MDA5-positive group showed the lowest 90-day survival rate (66.7%, anti-MDA5-positive; 100%, anti-ARS-positive; 100%, MSA-negative; $P < 0.01$). The anti-ARS-positive group had the highest 5-year survival rate (96%, anti-ARS-positive; 66.7%, anti-MDA5-positive; 68.3%, MSA-negative, $P = 0.02$). Univariate analysis revealed that anti-ARS antibody was associated with better prognosis (HR = 0.45; 95% CI, 0.18–0.89; $P = 0.02$), whereas anti-MDA5 antibody was associated with poorer prognosis (HR = 1.90; 95% CI, 1.02–3.39; $P = 0.04$).

Conclusions: The comprehensive MSA assessment demonstrated that anti-ARS and anti-MDA5 antibodies were two major MSAs, and the clinical features differed depending on MSA status in PM/DM-ILD. Assessment of anti-ARS and anti-MDA5 antibodies is practically useful for predicting clinical course and prognosis in PM/DM-ILD patients.

Abbreviation: ARS, aminoacyl tRNA-synthetase; BAL, bronchoalveolar lavage; CADM, clinically amyopathic dermatomyositis; CT, computed tomography; DM, dermatomyositis; GGA, ground-glass attenuation; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HRCT, high-resolution CT; ILD, interstitial lung disease; IP, immunoprecipitation; KL-6, krebs von den Lungen-6; MDA5, melanoma differentiation-associated gene 5; MAA, myositis-associated autoantibody; MSA, myositis-specific autoantibody; NSIP, nonspecific interstitial pneumonia; NXP-2, nuclear matrix protein 2; OP, organizing pneumonia; PM, polymyositis; SAE, small ubiquitin-like modifier activating enzyme; SP-D, surfactant protein-D; SRP, signal recognition particle; TIF1-γ, transcriptional intermediary factor 1-gamma; UIP, usual interstitial pneumonia.

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1. Introduction

Polymyositis (PM) and dermatomyositis (DM) are groups of idiopathic inflammatory myopathies that involve skeletal muscle, skin and/or other organs [1–3]. PM/DM patients present various clinical courses that are often complicated with interstitial lung disease (ILD), which is associated with poor prognosis [4–6]. A subgroup of PM/DM patients can develop rapidly progressive ILD, be refractory to glucocorticoid therapy and have fatal outcomes [6–12]. Therefore, the early recognition of high-risk patients is essential for determining the appropriate therapeutic strategy in PM/DM-ILD.

In PM/DM, the presence of serum myositis-specific autoantibody (MSA) is a key finding for diagnosis and classification [13]. Several MSAs, including anti-aminoacyl tRNA-synthetase (ARS), anti-melanoma differentiation-associated gene 5 (MDA5), anti-signal recognition particle (SRP), anti-transcriptional intermediary factor 1-gamma (TIF1-γ), anti-Mi-2, anti-small ubiquitin-like modifier activating enzyme (SAE), anti-nuclear matrix protein 2 (NXP-2) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies have been identified, and each MSA has been suggested to correlate with a distinct clinical phenotype [13–28]. Anti-ARS antibodies, including anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo and anti-Ha antibodies, are associated with a spectrum of characteristic manifestations, including ILD, myositis, arthritis, Raynaud's phenomenon and mechanic's hands, known as anti-synthetase syndrome [13,14,19–24,27]. In PM/DM-ILD, anti-ARS antibody-positive patients often experience a chronic course, respond to glucocorticoid therapy and have a better prognosis, but they sometimes relapse [14,27]. Anti-MDA5 antibody is exclusively detected in patients with DM or those with a distinct subgroup of clinically amyopathic DM (CADM) and is associated with skin ulcers, palmar papules and rapidly progressive ILD. In DM-ILD, anti-MDA5 antibody-positive patients are commonly resistant to glucocorticoid therapy and have a poor prognosis [16–18,25,26], although racial and regional differences have been suggested to affect the clinical courses [13,29–31].

The clinical significance of anti-ARS, anti-MDA5 and other myositis-specific antibodies has been individually evaluated in PM/DM. However, no reported study has investigated clinical features, including characteristics, symptoms, physical findings, laboratory data, high-resolution computed tomography (HRCT) images and prognosis, on the basis of comprehensive MSA assessment in PM/DM-ILD. Here we compared subgroups based on MSA status and determined the practical significance of MSAs in PM/DM-ILD patients.

2. Methods

2.1. Subjects

We retrospectively studied 60 consecutive PM/DM-ILD patients who were diagnosed between 1996 and 2015 in Hamamatsu University Hospital (Hamamatsu, Japan). This single-centre case-control study was conducted according to the Declaration of Helsinki and involved a retrospective review of clinical records. Signed consent forms to participate in this study were obtained from all patients, except those who had died, until March 2015. The institutional review board of Hamamatsu University School of Medicine waived the informed consent requirement for the deceased patients and approved this study (approval number E15-062). This information was posted on the website (http://hamamatsu-lung.com/study.html).

PM/DM was diagnosed according to Bohan and Peter's criteria [1,2]. In the present study, patients with definite or probable PM/DM were included. CADM was diagnosed as a distinct subgroup of DM when the patient had typical skin rash with little or no clinical evidence of myopathy during the study period [3,7,9,17,18,32]. Almost all of the patients underwent systemic examination of malignancies, and none had advanced malignancies at the time of initial diagnosis.

ILD was diagnosed on the basis of clinical presentation, physical examination, pulmonary function tests, HRCT images and/or lung biopsy findings [33–35]. Fifty-two (87%) patients underwent transbronchial lung biopsy and/or bronchoalveolar lavage (BAL) to diagnose ILD and rule out other lung diseases. No patients had other known causes of ILD or pulmonary infection at initial diagnosis. Disease onset was classified as ILD-preceding if ILD diagnosis preceded PM/DM diagnosis by >3 months, concomitant if ILD and PM/DM were diagnosed ≤3 months or myositis-preceding if PM/DM diagnosis preceded ILD diagnosis by >3 months [4,7].

ILD form was classified as acute (deteriorating < 1 month from the onset of respiratory symptoms or the initial visit), subacute (deteriorating 1–3 months) or chronic (stable or slowly progressive > 3 months) according to the clinical presentation [7,9].

2.2. Detection of myositis-specific autoantibodies

For all 60 PM/DM-ILD patients, the serum samples at the time of initial ILD diagnosis were available. The presence of MSAs, such as anti-ARS (anti-PL-7, Jo-1, PL-12, KS, EJ, OJ and other ARS antibodies), anti-MDA5, anti-SRP, anti- TIF1-γ, anti-Mi-2, anti-SAE, anti-NXP-2 and anti-HMGCR antibodies, and myositis-associated antibodies (MAAs), such as anti-SSA, anti-U1RNP, anti-Ku, and anti-PM-Scl antibodies, were measured by RNA-immunoprecipitation (IP) and protein-IP assays [17,28].

2.3. Review of radiographical findings

HRCT images taken at initial ILD diagnosis were reviewed. These images, composed of 1–2.5-mm collimation sections at 10-mm intervals, were reconstructed by a high spatial frequency algorithm and were displayed at window settings appropriate for viewing the lung parenchyma (window level, −600 to −800 Hounsfield units; window width, 1200–2000 Hounsfield units). Images were randomised and reviewed independently by two expert chest radiologists with 26 and 13 years of experience who were unaware of the related clinical information.

The HRCT patterns were classified as usual interstitial pneumonia (UIP), possible UIP, nonspecific interstitial pneumonia (NSIP), NSIP with organizing pneumonia (OP) and OP pattern according to the guidelines for idiopathic interstitial pneumonias with slight modification [33–36] (Supplementary Table 1). Patterns that could not be classified as those listed above were categorised collectively as unclassifiable CT pattern. Disagreements regarding HRCT interpretation were resolved by consensus agreement.

2.4. Statistical analysis

All values are expressed as the median (range) or a number (%). The observation period was calculated from the date of initial diagnosis of ILD (not PM/DM diagnosis) to the last visit or time of death. The 90-day survival rates were evaluated as the surrogate for initial treatment response. The Mann–Whitney *U* test and Fisher's test were used for comparing medians and proportions, respectively. Overall survival was evaluated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. When these statistical analyses showed significant results,