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Clinical Phenotype of Japanese Patients with Dermatomyositis

—Classification Based on Dermatomyositis-Specific Autoantibodies

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Abstract

Objectives: To correlate the precise specificity of autoantibodies in Japanese dermatomyositis (DM) patients with their clinical phenotypes. Methods: Serum samples from 94 adult DM patients (67 with classical DM and 27 with clinically amyopathic dermatomyositis, CADM) were screened for autoantibodies using immunoprecipitation assays. Patients with antibodies against aminoacyl transfer RNA synthetase (ARS), Mi-2 or who had other autoantibodies were assessed for clinical symptoms and laboratory findings. Results: Sera from 27 of 94 DM patients (29%) were found to have anti-ARS antibodies. Nineteen (20%) had anti-CADM-140/MDA5, 5 (5%) had anti-Mi-2, and 8 (6%) had anti-p155/TIF1-γ. Anti-MJ/NXP-2 was not found in our series of adult DM. Seventeen patients with anti-ARS had fever and 22 had arthritis and interstitial lung disease (ILD), compatible with a diagnosis of anti-ARS syndrome. Seventeen of 19 (89%) with anti-CADM-140/MDA5 had ILD, 16 (84%) of whom developed rapidly progressive ILD (RP-ILD). Four of 5 (80%) with anti-Mi-2 had heliotrope rash and/or Gottron's sign/papules, and 2 (40%) had V-sign and/or shawl-sign rash, whereas no ILD or malignancy was detected. As seen with anti-Mi-2-positive patients, a low frequency of ILD (13%) was found in patients with anti-p155/TIF1-γ but 6 of 8 (75%) had malignancy during their course. The frequency of ILD was significantly higher in patients with anti-ARS or anti-CADM-140/MDA5 compared with anti-Mi-2 or anti-p155/TIF1-γ (81% and 89%, respectively). It should be noted that anti-CADM-140/MDA5-positive patients suffered significantly more RP-ILD compared to patients with anti-ARS (84% vs. 7%, P < 0.0001). On the other hand, anti-p155/TIF1-γ positive patients had a significantly higher rate of ma-

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lignancy compared with anti-ARS-, anti-CADM-140/MDA5- and anti-Mi-2-positive patients (75% vs. 7%: P = 0.0004, 5%: P = 0.0006, 0%: P = 0.02, respectively). Conclusions: These results indicate that in addition to antibodies previously identified as specific for DM, autoantibodies newly found in these patients are useful for stratifying them into clinical subgroups.

Keywords

Dermatomyositis (DM), Interstitial lung Disease (ILD), Rapidly Progressive Interstitial Lung Disease (RP-ILD), Malignancy, Myositis-Specific Autoantibodies

1. Introduction

Dermatomyositis (DM) is a chronic inflammatory disorder that affects skin and muscle and is often accompanied by interstitial lung disease (ILD) or malignancy [1] [2]. The clinical manifestations are diverse in individual patients, reflecting subtypes of DM. Autoantibodies directed against aminoacyl transfer RNA synthetases (ARS), signal recognition particle (SRP), and Mi-2 are specific markers of polymyositis (PM)/DM [3] [4]. These well-known autoantibodies have proven clinically useful for the diagnosis and classification of PM/DM patients into subtypes and for predicting the response to treatment and prognosis.

Recently, new DM-specific autoantibodies have been discovered. Targoff *et al*. and Kaji *et al*. reported the presence of autoantibodies against a 155 kDa protein (anti-p155/TIF1-γ (transcriptional intermediary factor 1-γ antibodies) in patients with DM and found that they are closely associated with malignancy [5] [6]. We have identified autoantibodies against a 140 kDa protein (anti-CADM-140/MDA5 (melanoma differentiation-associated gene 5) antibodies) mainly in patients with clinically amyopathic dermatomyositis (CADM) [7] [8].

Although some clinical characteristics of Japanese DM patients with these newly-identified antibodies have been reported, thus far, correlations between the pattern of autoantibodies present and the patient's clinical course have been imprecise. In the present study, we investigated the variety of autoantibodies in Japanese DM patients in relation to their specificity and association with clinical phenotypes.

2. Methods

2.1. Patients and Sera

Serum samples from 94 Japanese patients with adult DM (67 with classical DM and 27 with CADM) who were seen at Keio University Hospital (2001-2008) and Tokai University Hospital (2010-2013) were screened for autoantibodies using immunoprecipitation (IP) assays. Blood samples were obtained after the patients had provided written informed consent approved by the Keio and Tokai University Institutional Review Boards.

2.2. Immunoprecipitation (IP)

The IP assay with K562 or HeLa cell extracts was performed as previously described [9]. For analysis of RNAs, antibodies bound to protein A-Sepharose CL-4B beads (Pharmacia Biotech AB, Uppsala, Sweden) were incubated with extracts of K562 or HeLa cells. They were then washed with NET-2 buffer (50 mM Tris-HCL, pH 7.5, 150 mM NaCl (Wako Pure Chemical Industries, Osaka, Japan), 0.05% Nonidet P-40 (Nacalai tesque, Kyoto, Japan). After ethanol precipitation, RNAs were dissolved in electrophoresis sample buffer composed of 10 M urea (Bio-Rad Laboratories, Hercules, CA), 0.025% bromophenol blue (Wako Pure Chemical Industries, Osaka, Japan), and 0.025% xylene cyanol-FF (Wako Pure Chemical Industries, Osaka, Japan) in TBE buffer (90 mM Tris-HCl, pH 8.6, 90 mM boric acid (Wako Pure Chemical Industries, Osaka, Japan), and 1 mM EDTA (Wako Pure Chemical Industries, Osaka, Japan)). The RNA samples were resolved in 7M urea-10% polyacrylamide gels, which were then silver stained (Bio-Rad Laboratories, Hercules, CA). For protein studies, antibody-coated Sepharose beads were mixed with [^{35}S] methionine-labeled K562 or HeLa extracts. After washing, the Sepharose beads were resuspended in SDS-sample buffer (2% SDS (Sigma, St. Louis, USA), 10% glycerol (Wako Pure Chemical Industries, Osaka, Japan), 62.5 mM Tris-HCl, pH 6.8, 0.005% bromophenol blue). The proteins were then fractionated by 10% SDS-PAGE and dried. Radiolabeled protein components were analyzed by autora-

diography. Anti-ARS, anti-SRP, anti-Mi-2, known myositis-specific antibodies, as well as anti-CADM-140/MDA5 and anti-p155/TIF1-γ are detectable with these assays by comparison with corresponding standard sera [10].

2.3. Clinical Features

The clinical symptoms, clinical course, and laboratory findings were retrospectively assessed from medical records in all patients including those positive for anti-ARS, anti-Mi-2, anti-CADM-140/MDA5 and anti-p155/TIF1-γ autoantibodies.

The diagnosis of DM was based on the diagnostic criteria proposed by Bohan and Peter [11]. The assessment of muscle weakness was performed according to a manual muscle test (MMT) [12]. The diagnosis of CADM was based on classification criteria proposed by Sontheimer *et al*. [13], *i.e*. DM patients with no clinical muscle symptoms for more than two years after the onset of skin manifestations. The remission of myositis was defined as both improvement of muscle strength on MMT and normalization of the serum creatine kinase (CK) value.

ILD was defined based on findings of chest radiography, chest CT, and lung function testing. Rapidly progressive ILD (RP-ILD) was defined as a subset of patients presenting progressive dyspnea along with hypoxemia and worsening of interstitial changes on the chest X-ray within one month of the onset of respiratory symptoms.

2.4. Statistical Analysis

All comparisons between each patient group were performed using Fisher's 2-tailed exact test or Student's t-test. Two-sided p-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Detection of Autoantibodies in Patients with DM

Using IP, we screened 94 DM patients´sera including 67 patients with classical DM and 27 with CADM. Myositis-specific autoantibodies (anti-ARS and anti-Mi-2) and myositis-associated autoantibodies (anti-SSA/Ro, anti-U1RNP) as well as recently identified autoantibodies (anti-CADM-140/MDA5, anti-p155/TIF1-γ) were studied. These proteins were easily distinguishable from those immunoprecipitated by sera reactive with other known antigens [14].

3.2. Frequencies of Autoantibodies in Patients with DM (Table 1)

Sera from 27 of the 94 DM patients (29%, 25 with classical DM and 2 with CADM) were found to contain

Table 1. Frequencies of autoantibodies in patients with DM.

	Dermatomyositis		
Autoantibodies n (%)	Classical DM	CADM	Total
	N = 67	N = 27	N = 94
Myositis-specific antibodies			
Anti-ARS	25 (37)	2 (7)	27 (29)
Anti-SRP	0 (0)	0 (0)	0 (0)
Anti-Mi-2	5 (7)	0 (0)	5 (5)
Myositis-associated antibodies			
Anti-SSA/Ro	8 (12)	2 (7)	10 (11)
Anti-U1RNP	4 (6)	0 (0)	4 (4)
Newly found DM-specific antibodies			
Anti-CADM-140/MDA5	2 (3)	17 (63)	19 (20)
Anti-p155/TIF1-γ	7 (10)	1 (4)	8 (9)
Anti-MJ/NXP-2	0 (0)	0 (0)	0 (0)
Negative	30 (45)	6 (22)	36 (38)

DM: dermatomyositis, CADM; clinically amyopathic dermatomyositis, ARS: aminoacyl tRNA sythetase, SRP: signal recognition particle.

anti-ARS antibodies (anti-Jo-1: 10; anti-EJ: 7; anti-PL-7: 5; anti-PL-12: 4; anti-OJ: 1). Five (5%) with classical DM had anti-Mi-2, 19 (20%, 2 with classical DM and 17 with CADM) had anti-CADM-140/MDA5, and 8 (9%, 7 with classical DM and 1 with CADM) had anti-p155/TIF1-γ antibodies. Interestingly, one patient with classical DM had both anti-Jo-1 and anti-p155/TIF1-γ antibodies. Anti-MJ/NXP-2 was not found in our series of adult DM; neither was anti-SRP, or PM-specific antibodies detected. Thus, overall, 58 of the 94 (62%) DM patients had myositis-specific antibodies.

3.3. Clinical Characteristics in Patients According to Possession of Each Autoantibody (Table 2)

3.3.1. Anti-ARS Antibodies

Of the anti-ARS antibody-positive patients, 25 had classical DM and 2 CADM. Anti-Jo-1 was the antibody most frequently present, followed by anti-EJ. Most patients had fever (63%), arthritis (81%) and Raynaud's phenomenon (30%). Twenty-two patients (81%) had ILD and 20 of these (91%) had a chronic course. These clinical features are consistent with the anti-ARS syndrome previously proposed.

3.3.2. Anti-CADM-140/MDA5 Antibodies

Similar to anti-ARS antibody-positive patients, many of those with anti-CADM-140/MDA5 antibodies had fever (68%), arthritis (79%) and ILD (89%). However, in contrast to anti-ARS-positive patients, 16 of 17 (94%) with ILD developed RP-ILD. Treatment with high-dose prednisolone including pulse therapy with intra-venous intermittent cyclophosphamide and/or cyclosporine A was given to all 16 RP-ILD patients, with respiratory symptom improvement in 12 (75%).

3.3.3. Anti-Mi-2 Antibodies

All 5 Mi-2-antibody-positive patients were diagnosed as classical DM with obvious muscle weakness and serum CK elevation. Steroid therapy for muscle symptoms was started and all patients improved. Four of 5 (80%) had typical DM skin manifestations, heliotrope rash and/or Gottron's sign/papules and 2 (40%) had V-sign or shawl-sign rash. No ILD or malignancy was detected in any of these patients.

3.3.4. Anti-p155/TIF1-γ Antibodies

A relatively high frequency of V-sign and/or shawl-sign rash (63%) and a low frequency of ILD (13%) were found in patients with anti-p155/TIF1-γ antibodies. It is noteworthy that 6 of 8 (75%) had malignancy (bladder, gastric, lung, ovarian, peritoneal cancer, malignant lymphoma) during their course.

Table 2. Comparison of clinical features in DM patients with each autoantibodies.

Clinical and laboratory findings	Anti-ARS	Anti-CADM-140/MDA5	Anti-Mi-2	Anti-p155/TIF1-γ	Negative
	(n = 27)	(n = 19)	(n = 5)	(n = 8)	(n = 36)
Age at onset (mean ± SD)	52 ± 14	53 ± 13	55 ± 17	62 ± 20	51 ± 14
Male/female	8/19	5/14	2/3	2/6	7/29
Gottron's sign or papules (%)	67	84	80	88	78
Heliotrope rash (%)	37	37	80	38	56
V-sign or Shawl-sign (%)	15	37	40	63	31
Muscle weakness (%)	93	11	100	88	81
Elevation of CK (%)	93	26	100	88	78
Fever (%)	63	68	20	25	53
Arthritis (%)	81	79	60	13	50
Raynaud's phenomenon (%)	30	5	0	13	6
ILD (%)	81	89	0	13	50
Rapidly progressive ILD (%)	7	84	0	0	8
Malignancy (%)	7	5	0	75	19
ANA (FANA) (%)	44	16	100	88	36

CK= creatine kinase; ILD = interstitial lung disease; ANA = anti-nuclear autoantibodies.

3.4. Comparison of Clinical Features in Patients Relative to Each Autoantibody

The frequency of V-sign or shawl-sign rash in patients with anti-p155/TIF1-γ was significantly higher than in patients with anti-ARS (15% vs. 63%: P = 0.015). The frequency of ILD was significantly higher in patients with anti-ARS or anti-CADM-140/MDA5 in comparison with anti-Mi-2-positive (81% vs. 0%: P = 0.0013, 89% vs. 0%: P = 0.0005, respectively) and anti-TIF1-γ positive patients (81% vs. 13%: P = 0.0008, 89% vs. 13%: P = 0.003, respectively). Moreover, it should be noted that anti-CADM-140/MDA5-positive patients suffered significantly more RP-ILD compared to patients with anti-ARS (7% vs. 84%, P < 0.0001). Interestingly, anti-p155/TIF1-γ positive patients had a significantly higher rate of malignancy than anti-ARS-, anti-CADM-140/MDA5- or anti-Mi-2-positive patients (75% vs. 7%: P = 0.0004, 5%: P = 0.0006, 0%: P = 0.02, respectively).

4. Discussion

We surveyed autoantibodies in Japanese patients with DM and analyzed the association between clinical characteristics and antibody specificity. We found a close association between clinical features and the presence of each particular autoantibody specificity.

In our series, 58 of 94 (62%) patients with DM possessed at least one DM-specific antibody (anti-ARS, anti-Mi-2, anti-CADM-140/MDA5 or anti-p155/TIF1-γ). This is a slightly higher rate than in previous reports. Hamaguchi *et al*. reported the presence of these antibodies in 147 of 376 (39%) patients [15] and Ikeda *et al*. found them in 29 of 55 (53%) patients [16]. Thus, the discovery of new DM-specific antibodies in recent years enables us to classify more than half of all DM patients into specific clinical entity groups and to predict their prognosis. Moreover, these antibodies are useful for making a correct diagnosis in daily clinical practice.

We tried to make the clinical subtyping of DM patients using DM-specific autoantibodies more accurate (**Table 3**). Eight autoantibodies to ARS have been described so far, the most frequent being anti-Jo-1 antibody. Anti-ARS antibodies are known as being specific for PM/DM patients although some of these antibodies seem to have stronger associations with ILD. Interestingly, these anti-ARS-positive patients had common clinical manifestations such as fever, arthritis, Raynaud's phenomenon, mechanic's hand and chronic ILD. They represent patients with "anti-ARS syndrome". Therefore, anti-ARS autoantibodies are common in classical DM with a high frequency of fever, arthritis, and chronic ILD. On the other hand, anti-CADM-140/MDA5 antibody is more frequently detected in CADM patients especially in Japan. The most striking characteristic of the presence of this antibody is its strong association with RP-ILD, a DM complication with poor prognostic implications. Because it is likely that early diagnosis and treatment is important in this condition, measuring anti-CADM-140/MDA5 antibody could significantly benefit DM and RP-ILD patients. Patients with anti-Mi-2 antibody tended to have typical DM skin manifestations (Heliotrope rash or Gottron's sign and/or papules). Complications that affect their prognosis such as ILD or neoplasia seem to occur with very low frequency. In this respect,

Table 3. Clinical subtyping using DM-specific autoantibodies.

Clinical and laboratory findings	Anti-ARS	Anti-CADM-140/MDA5	Anti-Mi-2	Anti-p155/TIF1-γ
Typical DM rash			○	
V-sign or Shawl-sign				○
Muscle weakness	○	×	○	○
Elevation of CK	○	×	○	○
Fever	○	○	×	×
Arthritis	○	○	×	×
Rapidly progressive ILD	×	○	×	×
Chronic ILD	○	×	×	×
Malignancy			×	○
ANA (FANA) positive (%)	×	×	○	○

CK = creatine kinase; ILD = interstitial lung disease; ANA = anti-nuclear autoantibodies; ○ = relatively frequent; × = relatively low frequent or rare.

patients with anti-Mi-2 antibody have a relatively good prognosis. Finally, anti-p155/TIF1-γ is detected in both classical DM and CADM with DM typical skin rash as well as V-sign and/or Shawl-sign. Patients with this antibody have a high frequency of malignancy which should therefore be considered at the time of diagnosis.

5. Conclusion

New autoantibodies specifically found in DM as well as previously well-known DM-specific antibodies are useful for classifying DM patients into clinical subgroups as well as for differential diagnosis, choice of treatment and prediction of outcome in daily clinical practice. Further efforts to discover new DM-specific antibodies will facilitate progress in the clinical management of DM.

Disclosures

None by all authors.

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Abbreviations

PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathicdermatomyositis; ARS: aminoacyl transfer RNA synthetase; TIF1-γ: transcriptional intermediary factor 1-γ; MDA5: melanoma differentiation-associated gene 5; ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; IP: immunoprecipitation; MMT: manual muscle test; CK: creatine kinase.