Mini Review

Anti-CADM-140/MDA5 antibody and clinical subsets of dermatomyositis

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The clinical features of dermatomyositis (DM) have a close relationship with myositis-specific antibodies. Clinically amyopathic dermatomyositis (CADM) is a subgroup of DM, which manifests as characteristic skin symptoms compatible with DM, such as Gottron's sign and heliotrope rash with no or mild muscle symptoms. Sometimes, a life-threatening rapidly progressing interstitial lung disease can complicate CADM. In recent years, anti-CADM-140/MDA5 antibodies have been observed in serum obtained from patients with CADM. Thus, measurement of anti-CADM-140/MDA5 antibodies is useful for the diagnosis and prediction of prognosis of patients with CADM.

Rec.4/8/2013, Acc.5/10/2013, pp223-227

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Key words amyopathic dermatomyositis, anti-CADM-140/MDA5 antibody

Introduction

Dermatomyositis(DM) is an inflammatory myopathy of unknown etiology characterized by myalgia, muscle weakness and pain of the proximal muscles when grasping objects, elevated muscle enzyme levels and characteristic skin symptoms such as Gottron's sign and heliotropic rash. Myositis-specific antibodies(MSAs), such as anti-aminoacyl tRNA synthetases antibodies (Abs), are found in patients with DM. MSAs are useful for the classification and diagnosis of DM.

Amyopathic dermatomyositis(ADM) is a subgroup of DM, which manifests characteristic skin symptoms compatible with DM such as Gottron's sign and heliotrope rash without muscle symptoms, lack of electromyography abnormalities and elevated serum creatine kinase(CK) levels[1]. In 2002, Sontheimer et al. advocated the concept of "clinically amyopathic dermatomyositis(CADM)", which integrated ADM and hypomyopathic DM (DM with mild muscle symptoms)[2].

DM is often complicated by interstitial lung disease(ILD),

which is a major prognostic factor for DM. Analysis by Lakhanpal et al. revealed that approximately 39% of polymyositis/DM cases were complicated by ILD[3]. ILD in patients with CADM is often presents as a rapid progress interstitial lung disease(RPILD), which can be fatal[4]. Suda et al. reported that patients with RPILD associated with CADM showed poor prognosis with a 5-year survival of 35%. Interestingly, most deaths were within 2 months of disease onset[5].

Analysis of patients with CADM/classical DM complicated with ILD who were hospitalized between 2001 and 2007 at Nagasaki University Hospital revealed that patients with CADM had a lower PaO_2/FiO_2 ratio due to the rapid progression of respiratory failure, higher lymphocyte subset ($CD4^+/CD8^+$) ratios than patients with classical DM and a higher mortality rate than patients with CADM[6]. Suda et al. analyzed surgical biopsy specimen of CADM lung, and reported most common findings of microscopic examination were nonspecific interstitial pneumonia[5].

The diagnosis of CADM at early stages where only skin symptoms and dyspnea present might be difficult, therefore it is important to identify useful markers for the early diagnosis of CADM.

Anti-CADM-140 Abs determined by immunoprecipitation(IP) and predicting the prognosis of CADM

In 2005, Sato et al. detected autoantibodies that recognized a 140 kDa polypeptide in 8 of 42 patients with DM. Patients positive for anti-CADM-140 antibodies showed a lower frequency of muscle weakness, lower serum CK levels and a higher frequency of RPILD, which were characteristic of CADM. They named the antibody "anti-CADM-140 antibodies", which was considered useful as a serum marker for patients with CADM[7]. In addition, it was very interesting to note that DM patients with anti-CADM-140 antibodies were more likely to have RPILD compared with patients lacking anti-CADM-140 antibodies.

Table 1 Comparison of the clinical and laboratory characteristics of anti-155/140 Ab-positive and anti-140 Ab-positive patients with anti-aminoacyl tRNA synthetase (ARS) Ab-positive patients

	Anti-155/140 Ab-positive (n=5)	Anti-140 Ab-positive (n=8)	Myositis-specific Ab-negative (n=10)	Anti-ARS Ab-positiv (n=7)
Age at onset (years), mean ±SD	67.8 ±9.9	60.5 ±10.9	50.3 ±16.7	52.0 ±16.3
Number of males/females	4/1	1/7	2/8	1/6
Skeletal muscle and skin feathers, n (%)				
Muscle weakness	3(60)	2(25)	6(60)	6(86)
Gottron's sign	5(100)	7(88)	6(60)	3(43)
Palmer papules	0	5(63)	1(10)	0
Heliotrope rash	4(80)	3(38)	5(30)	5(71)
Periungual erythema	0	5(63)	2(20)	1(14)
Clinical diagnosis, n (%)				
Classical DM	3(60)	2(25)	6(60)	6(86)
CADM	2(40)	6(75)	4(40)	1(14)
Pulmonary involvement and malignancy, n (%)				
ILD	1(20)	8(100)	7(70)	7(100)
Rapidly progressive ILD	0	8(100)	2(20)	0
Mediastinal emphysema	0	40(50)	0	0
Malignancies	5(100)	0	0	0
Laboratory data				
CPK (IU/L), mean ±SD	4100 ±4173	219 ±186	1988 ±2010	1483 ±1292
KL-6(U/mL), mean ±SD	ND	2057 ±936	694 ±513	1310 ±661
PaO_2/FiO_2 (mmHg), mean ±SD	ND	143 ±82	338 ±81	351 ±67
Therapy				
Therapy weeks, mean ±SD	4.0 ±0.7	3.6 ±2.1	7.4 ±3.0	8.3 ±4.7
Maximum PSL (mg/day), mean ±SD	34.0 ±24.1	51.3 ±31.5	40.5 ±15.7	45.7 ±9.8
Steroid pulse, n (%)	2(40)	8(100)	7(70)	3(43)
Immunosuppressant, n (%)	2(40)	8(100)	8(80)	4(57)
Outcome, n(%)				
Death	2(40)	6(75)	0	0

Ab, antibody; SD, standard deviation; n, number; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; CPK, creatine phosphokinase; KL-6, mucin 1, cell surface associated; ILD, interstitial lung disease; ND, not done; PSL, prednisolone; IU, international units; U, units; FiO_2, fractional inspired oxygen concentration; PaO_2, partial pressure of arterial oxygen.

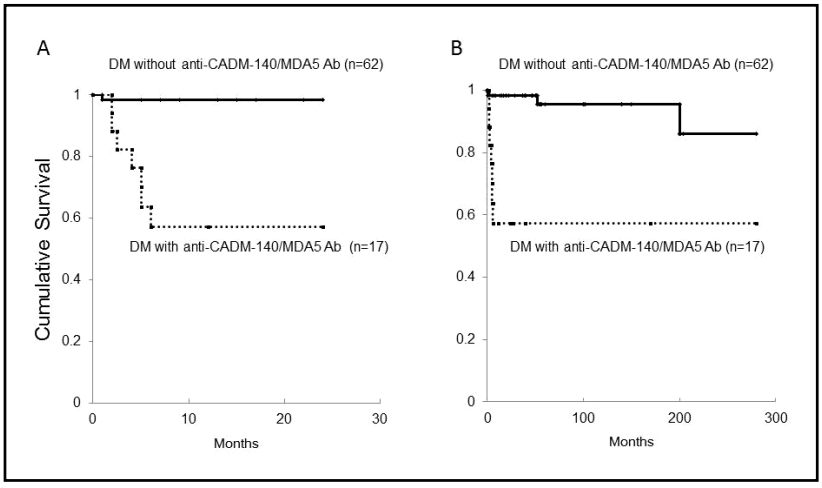

Fig.1 Kaplan-Meier survival curves show differences in cumulative survival between DM patients with and without anti-CADM-140/MDA5 Abs

(A):Short-term prognosis of DM patients. Differences in mortality were significant at 6 months from the diagnosis of DM. (B):Long-term prognosis of DM patients. Patients' positive for anti-CADM-140/MDA5 Abs who survived the first 6 months from diagnosis of CADM did not die of respiratory failure until 60 months after diagnosis of CADM. DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis.

We analyzed the association of clinical subsets of DM with MSAs. To confirm this, we analyzed the clinical features and autoantibody profile of patients with DM by IP. The study population consisted of 30 patients with DM, including 5 patients with anti-155/140-kDa Abs, 8 patients with anti-140-kDa Abs, 7 with anti-ARS Abs and 10 MSAs-negative patients. The analysis revealed that all of 5 patients with anti-155/140-kDa Abs had complications of malignancy and all of 8 patients with anti-140-kDa Abs had complications of RPILD. In addition, patients with anti-140-kDa Abs had a high mortality rate at 6 months from diagnosis (6 patients died of respiratory failure within 6 months of diagnosis) (Table 1)[8].

Anti-CADM-140/MDA5 Ab determined by enzyme-linked immunosorbent assay (ELISA) and predicting the prognosis of CADM

In 2009, Sato et al. reported that (melanoma differentiation-associated gene 5) MDA5 was the corresponding target antigen for anti-CADM-140 antibodies[9]. They compared the results of testing for anti-CADM-140/MDA5 autoantibody by ELISA with the results obtained from an IP assay. The positive rate by ELISA was similar with that of the IP assay: an analytical sensitivity of 85% and analytical specificity of 100% was observed when compared with the IP assay (all sera positive for anti-CADM-140/MDA5 Ab by ELISA were also positive in the IP assay, three of the 27 positive for anti-CADM-140/MDA5 autoantibody by IP assay were negative by ELISA), which confirmed the detection of anti-CADM-140/MDA5 autoantibodies by ELISA.

We analyzed the association between CADM patients positive for anti-CADM-140/MDA5 Abs determined by ELISA and their prognosis[10]. The study population consisted of 79 patients with DM, including 21 patients with CADM and 58 patients with classical DM. Seventeen of 19 patients and none of the 58 patients were positive for anti-MDA5 Abs. Similar to patients with anti-140-kDa Abs, patients positive for anti-CADM-140/MDA5 Abs had a high mortality rate at 6 months from diagnosis of CADM, and a main cause of death was respiratory failure. However, patients' positive for anti-CADM-140/MDA5 Abs who survived the first 6 months from diagnosis of CADM did not die of respiratory failure until 60 months after diagnosis of CADM. This was due to the fact that relapse of RPILD was not observed in the study patients. Our analysis showed that the measurement of anti-CADM-140/MDA5 Abs was useful for predicting the prognosis of patients with CADM. In addition, the long-term prognosis of patients with anti-CADM-140/MDA5 Abs who survived the first 6 months from diagnosis of CADM was not necessarily bad, which was compatible with our previous analysis regarding anti-CADM-140 Abs (Fig.1)[7, 10]. Furthermore, we compared the variables (age at onset, gender, presence of ulcer region, palmar papules, serum creatine kinase levels, titers of anti-CADM-140/MDA5 Abs, PaO_2/FiO_2 before treatment, intravenous pulse steroid therapy, administration of cyclophosphamide, administration of oral calcineurin inhibitor and administration of intravenous calcineurin inhibitor) between patients positive for anti-CADM-140/MDA5 Abs who were alive or dead. There was a statistically significance difference in serum CK levels, titers of anti-CADM-140/MDA5 Abs and PaO_2/FiO_2 before treatment, between patient groups who were dead or alive. There was no statis-

Table 2 Comparison of clinical parameters between anti-CADM-140/MDA5 antibody patients who were dead or alive

Variable	Alive (n=10)	Dead (n=7)	P-value
Age at onset, years	52 (42-58.5)	59 (53-70)	0.051
Female, n (%)	9 (90)	6 (86)	1.00
Ulcer region, n (%)	5 (50)	5 (71)	0.70
Palmar papules, n (%)	7 (70)	5 (71)	1.00
CPK, IU/L	208 (90.3-864)	169 (33.5-359)	0.014
Anti-CADM-140/MDA5 antibody titler	168 (16.3-436)	230 (76.0-478)	0.032
PaO_2/FiO_2 before treatment, mmHg	395 (370-462)	203 (114-240)	0.027
Therapy Steroid pulse therapy, n (%) Cyclophosphamide, n (%) Oral calcineurin inhibitor, n (%) I.V. calcineurin inhibitor, n (%)	 5 (50) 4 (40) 6 (60) 1 (10)	 7 (100) 4 (57) 7 (100) 3 (43)	 0.09 0.84 0.18 0.32

CPK, creatine phosphokinase; CADM, clinically amyopathic dermatomyositis; IU/l, international units per liter; FiO_2, fractional inspired oxygen concentration; PaO_2, partial pressure of arterial oxygen; I.V., intravenous.

tically significant difference for the type of therapy between the 2 patient groups (Table 2)[10]. Gono et al. reported patients with anti-CADM-140/MDA5 antibody and ≧1,600 ng/ml ferritin levels showed higher mortality rate than patients with anti-CADM-140/MDA5 antibody and less than 1,600 ng/ml serum ferritin levels[11].

It has been debated whether aggressive immunosuppressive therapy improves the prognosis of patients with CADM. According to our analysis, the mean PaO_2/FiO_2 levels before the introduction of immunosuppressive therapy was a major prognostic factor, suggesting that the early introduction of immunosuppressive therapies is beneficial for lifesaving in CADM, irrespective of the doses and types of regimes used. Recently, it was reported that titers of anti-CADM-140/MDA5 autoantibody measured by ELISA correlated with clinical severity in CADM. Thus, CADM patients who died had higher titers of anti-CADM-140/MDA5 autoantibodies than CADM patients who survived. In addition, a decline in anti-CADM-140/MDA5 autoantibody titers was observed in CADM patients who responded to immunosuppressive therapy[12]. These observations suggested that high titers of anti-CADM-140/MDA5 autoantibodies predict a more severe disease course and resistance to immunosuppressive therapy in patients with CADM. We previously described two CADM cases with relatively high titers of anti-CADM-140/MDA5 autoantibodies successfully treated with early immunosuppressive therapy[13].

Although the pathogenesis of CADM is not fully clarified, it is speculated virus infections have important roles based on the fact that MDA5 plays important roles in the innate immune recognition during RNA virus infection[14]. Further studies are warranted to elucidate the relationship between the intensity of immunosuppression, intervals between diagnosis and treatment initiation and titers of anti-CADM-140/MDA5 autoantibodies.

Conclusion

The measurement of MSAs is thought to be useful for determining the diagnosis and prognosis of patients with DM. Particularly, the measurement of anti-CADM-140/MDA5 Abs in patients who might have CADM is important because fatal RPILD often complicates CADM. Patients with CADM have a high risk of RPILD, which is often life-threatening. Therefore, early diagnosis and treatment with aggressive immunosuppressive therapies are required to improve the prognosis of CADM.

Acknowledgements

We would like to thank Masataka Kuwana (Division of Rheumatology, Department of Internal Medicine, Keio University School of

Medicine), Yasuhito Hamaguchi and Manabu Fujimoto (Department of Dermatology, Graduate School of Medical Science, Kanazawa University) for measuring anti-CADM-140/MDA5 Abs by IP and ELISA.

Sources of Funding

None

Conflict of interest statement

The authors declare that they have no conflict of interest.

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