Anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis exhibit three clinical phenotypes with different prognoses

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Abstract

Objective

We aimed to identify different subtypes of dermatomyositis (DM) patients positive with anti-melanoma differentiation-associated gene 5 antibody (DM-MDA5$^+$) for customised treatments to improve the outcomes.

Methods

Among 96 DM-MDA5$^+$ patients, subgroups with similar phenotypes were delineated using hierarchical clustering analysis of the clinico-biological characteristics. Classification and regression trees were used to build a classification model and survival analysis was used to evaluate the prognoses of subgroups.

Results

Three subgroups were identified among 96 DM-MDA5$^+$ patients, and patients in different subgroups had highly heterogenic manifestations and outcomes. Cluster 1 patients were referred to as mild group of rheumatologic patterns with good prognosis. Cluster 2 patients were referred to as young typical DM group with good prognosis. Cluster 3 patients were referred to as elderly rapidly progressive interstitial lung disease (RPILD) group with poor prognosis. A predictive model to classify patients was established, and three critical factors were found, including age, serum ferritin and myalgia.

Conclusion

DM-MDA5$^+$ patients have a poor short-term prognosis. Three clinical phenotypes with different prognoses were identified in DM-MDA5$^+$ patients.

Key words

anti-melanoma differentiation-associated protein-5, clinical phenotypes, interstitial lung disease, dermatomyositis, predictor

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous autoimmune diseases that can affect skin, muscles and extra-muscular organs (1). Interstitial lung disease (ILD) is the most frequent extra-muscular manifestation, and rapidly progressing ILD (RPILD) is the leading cause of mortality. Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a myositis specific antibody (MSA) identified in 2005 (2). Since then, many studies have demonstrated that dermatomyositis (DM) patients positive with anti-MDA5 antibody (DM-MDA5$^+$) have significantly higher incidence of developing ILD and RPILD compared to patients positive with other MSAs, resulting in poor prognosis (3, 4).

Emerging clinical findings suggest there may be different subtypes of DM-MDA5$^+$patients, and clinical features and prognosis may vary among different subtypes. It is reasonable to postulate that specific prognosis predictors may exist and customised treatments may be used. Early and aggressive interventions for those with poor prognosis may effectively reduce their mortality. Our current study aimed to delineate clinical features and identify reliable predictors for mortality in different subtypes of DM-MDA5$^+$ patients in order to improve the treatment outcomes.

Methods

Patient enrolment

Patients who were diagnosed with DM or clinically amyopathic DM (CADM) with anti-MDA5 positivity for the first time at the First Affiliated Hospital of Zhengzhou University from 2018 to 2019 were included in this cohort. Anti-MDA5 antibody was detected using line-immunoassays (Euroimmun, Germany). The exclusion criteria included: 1) age <16 years, 2) complicated with other connective tissue diseases, 3) incomplete clinical or laboratory data necessary for this study. The diagnosis of DM was based on Bohan and Peter criteria (5, 6), and CADM was based on Sontheimer criteria (7). This study was in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (no. 2020-KY-194).

Data collection

The data of the patients were retrospectively collected without any missing values, including gender, age, disease duration, clinical manifestations, laboratory results and high-resolution CT (HRCT) findings. RPILD was defined as follows: deteriorating dyspnoea on exertion, decrease in arterial oxygen partial pressure (PaO_2) levels by >10 mmHg within 4 weeks, or expanding ground grass opacification (GGO) on HRCT within 4 weeks. The survival status during the first 6-months follow-up were retrospectively recorded.

Statistical analysis

A multiple correspondence analysis was firstly used as a multivariate statistical method to reduce the dimensions of the data set. The principal components were set to minimise the overfitting effect, and the mean square error of prediction (MSEP) appeared to be a well-fitted criterion to select the number of components. We performed K-fold cross-validation to obtain the number of components leading to the smallest MSEP and performed multiple runs to avoid overfitting. The second step was a hierarchical clustering onto the principal components. A hierarchical tree was built using Ward's criterion. In the third step, partitioning (setting the number of clusters) was finally performed. Qualitative variables were presented as counts and percentages and compared between groups using the Pearson's Chi-squared test or Fisher's exact test.

The classification and regression trees were used to construct a decisional algorithm tree to position the patients in a cluster. For the survival analysis, Kaplan-Meier analysis with the log-rank test was performed on different patient subgroups. Statistical analysis was performed using R software (v. 4.0.5, USA) and MedcCalc software (v. 18.2.1, Belgium). The significance levels were computed for 2-tailed testing and the cut-off of significance was set at $p<0.05$.

Table I. Characteristics of 3 clusters of anti-MDA5 antibodies positive DM patients.

	Cluster 1 (n=39)	Cluster 2 (n=13)	Cluster 3 (n=44)	*p*
Female, n. %	10 (25.6)	7 (53.8)	17 (38.6)	0.148
Age ≥55 years, n. %	11 (28.2)	0 (0)	32 (72.7)	0.002*
Fever, n. %	14 (35.9)	7 (53.8)	34 (77.3)	0.001*
Arthritis, n. %	33 (84.6)	8 (61.5)	28 (63.6)	0.059
Muscle weakness, n. %	10 (25.6)	12 (92.3)	33 (75.0)	0.000*
Myalgia, n. %	3 (7.7)	9 (69.2)	23 (52.3)	0.000*
Mechanic's hand, n. %	20 (51.3)	2 (15.4)	15 (34.1)	0.050*
Heliotrope sign, n. %	23 (59.0)	9 (69.2)	27 (61.4)	0.805
V neck sign, n. %	7 (17.9)	9 (69.2)	5 (11.4)	0.000*
Shawl sign, n. %	0 (0)	8 (61.5)	1 (2.3)	0.000*
Gottron's papules, n. %	24 (61.5)	7 (53.8)	34 (77.3)	0.158
Raynaud's phenomenon, n. %	6 (15.4)	0 (0)	3 (6.8)	0.292
Skin ulcers, n. %	0 (0.0)	0 (0)	2 (4.5)	0.624
Anti-Ro52 antibodies, n. %	24 (61.5)	9 (69.2)	36 (81.8)	0.116
Ferritin ≥1000 ug/L, n. %	5 (12.8)	4 30.8)	33 (75.0)	0.000*
Elevated CK, n. %	1 (2.6)	5 (38.5)	9 (20.5)	0.002*
Increased ESR or CRP, n. %	29 (74.4)	7 (53.8)	44 (100.0)	0.000*
RP-ILD, n. %	3 (7.7)	1 (7.7)	34 (77.3)	0.000*

CK: creatine kinase; RP-ILD: rapidly progressive interstitial lung disease.

Results

Characteristics of anti-MDA5 antibody positive patients

This study included 96 DM-MDA5$^+$ patients with 34 males (35.4%) and 62 females (64.6%), and with a median age of 52 (45.0, 59.5) years old. Among them, 72 patients were diagnosed with CADM (75.0%) and 24 patients with DM (25.0%). The disease duration ranged from 0.5 to 72 months, with a median course of 2.0 (1.0, 4.0) months. Based on HRCT findings, 89 patients (92.7%) had ILD of varied degrees on admission. During the 6-month follow-up period, 38 patients (39.6%) developed RPILD and 25 patients (26.0%) died of respiratory failure caused by ILD or RPILD complicated with infections.

Characteristics of 3 clusters of DM-MDA5$^+$ patients

Hierarchical cluster analysis was performed and all DM-MDA5$^+$ patients were divided into 3 clusters (Table I). The factorial plot based on multiple correspondence analysis showed that the distribution of patients of 3 clusters was relatively concentrated and mutually exclusive (Fig. 1).

Patients in cluster 1 (n=39, 40.6%) had the highest incidence of arthritis (84.6%) and mechanic's hand (51.3%), and lowest incidence of RPILD (7.7%), muscle weakness (25.6%), myalgia (7.7%), fever (35.9%), elevated CK (2.6%) and serum ferritin ≥1000 ug/L (12.8%) (all $p<0.05$). Only one patient (2.6%) died in this group. Cluster 1 patients were referred to as mild group of rheumatologic patterns with good prognosis.

Cluster 2 (19 patients, 19.8%) had the highest incidence of shawl sign (69.2%), V-neck sign (69.2%), muscle weakness (92.3%), myalgia (69.2%) and elevated CK (38.5%) and lowest incidence of RPILD (all $p<0.05$). All patients in this cluster were younger than 55 years. No patient died in this group. Cluster 2 patients were referred to as young typical DM group with good prognosis.

Cluster 3 (44 patients, 45.8%) had the highest incidence of RPILD (77.3%), fever (77.3%), elevated ESR or CRP (100%), and serum ferritin ≥1000 ug/L (75%) (all $p<0.05$). In addition, a large majority of patients in this cluster were over 55 years old (72.7%). Twenty-four patients (54.5%) died, and the mortality rate (54.5%) was significantly higher than that in cluster 1 and 2 ($p<0.01$). Thus, cluster 3 was referred to as elderly RPILD group. The survival curves

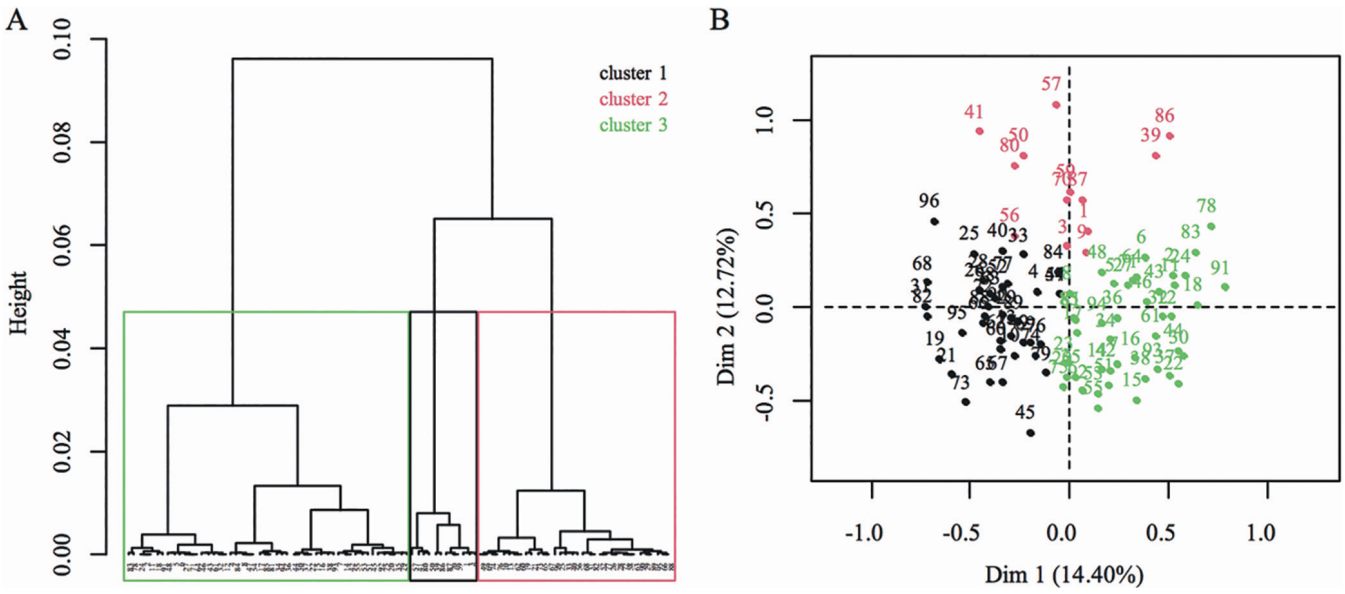

Fig. 1. A: Hierarchical cluster analysis of DM-MDA5$^+$ patients. **B**: Multiple correspondence analysis confirmed the presence of 3 clusters of DM-MDA5$^+$ patients.

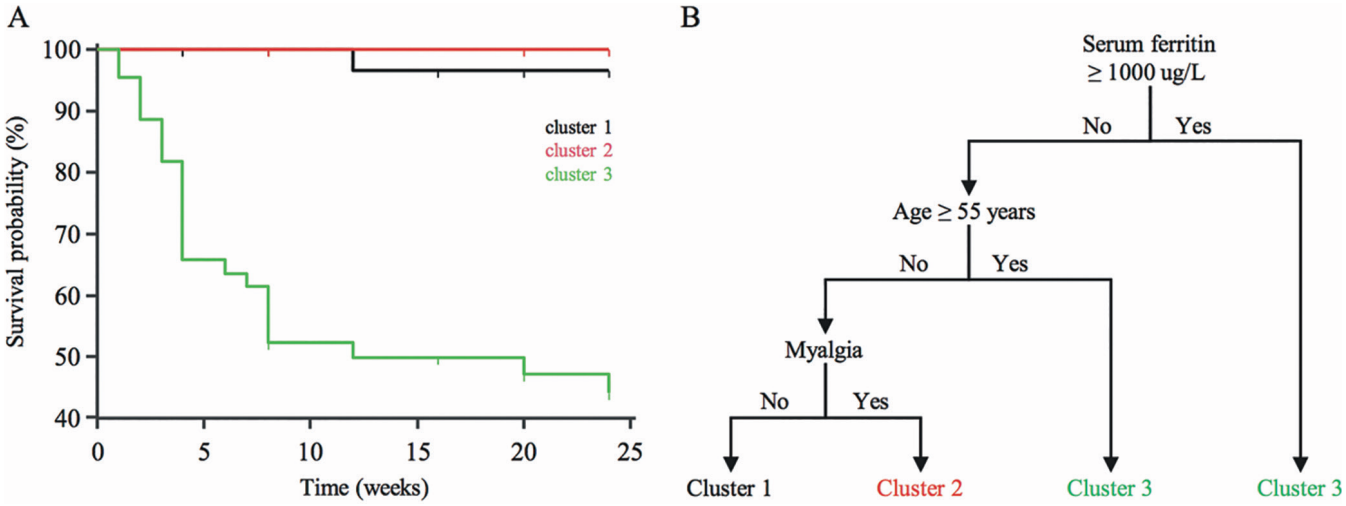

Fig. 2. A: Survival curves of 3 clusters of DM-MDA5⁺ patients. **B**: According to classification algorithm regression tree analysis, serum ferritin, age and myalgia were included into the prognosis model.

showed that patients in cluster 3 had the worst prognosis compared to patients in cluster 1 and 2 ($p<0.05$) (Fig. 2A).

As RPILD was closely associated with the prognosis, other 17 items, except for RPILD, were included into the classification and regression tree analysis in order to establish a predictive model. Three critical factors were finally used in this model including age, serum ferritin and myalgia, and the prediction accuracy of this model was 74.0% (Fig. 2B).

Discussion

In this study, we identified 3 subtypes of DM-MDA5⁺ patients: mild rheumatologic pattern, young typical DM pattern and elderly RPILD pattern. The mortality rates vary significantly among these 3 subtypes with the elderly RPILD group patients being the highest.

By hierarchical cluster analysis, 96 DM-MDA5⁺ patients were divided into 3 clinical phenotypes. Cluster 1 was characterised by mechanic's hand and arthritis, and RPILD was rarely seen. Cluster 2 manifested as typical DM at relatively young age. Both groups had good prognosis, mainly due to low incidence of RPILD. Patients in cluster 3 had elderly age at the onset of disease and high incidence of RPILD, thus with the worst prognosis. Based on the results of classification and regression analysis, patients can be categorised into one of these three clusters according to age, myalgia and serum ferritin level. Previous studies have demonstrated that there are at least 3 clinical phenotypes in DM-MDA5⁺ patients: 1) cutaneous form without muscle or lung involvement, 2) chronic form of cutaneous features with ILD resembling the antisynthetase syndrome, and 3) the most severe form with RPILD (4, 8-10). In a French myositis cohort, DM-MDA5⁺ patients were also divided into 3 phenotypes: RPILD group, rheumatoid group and vasculopathic group (11). Compared to the French study, we did not find patients with characteristic features with the vasculopathic phenotype. We postulate that several factors may contribute to such discrepancy. Significant differences in common manifestations were noticed between our study and the French study: fever (57.3% *vs*. 24.0%), skin ulcer (2.1% *vs*. 31.4%) and ILD (92.7% *vs*. 51.8%), suggesting there may exist ethnic differences in DM-MDA5⁺ patients. In addition, all of our patients were recruited from a single centre of a tertiary hospital, while the French cohort was a multi-centre study.

Our initial goal was to identify some reliable factors to predict the prognosis of patients with different clinical features. However, as the classification algorithm regression tree analysis have demonstrated that the prognosis was good in both cluster 1 and 2 patients, we designate the poor predictors as patients aged over 55 years or serum ferritin above 1000 ug/L. These two factors have been validated with new statistical method, confirming the previous findings (3, 12, 13). One explanation is that pulmonary macrophages are important players in the progression of ILD (14, 15). Therefore, high serum ferritin level, a marker of exaggerated macrophage activation, is closely associated with development of RPILD. To the best of our knowledge, this is the first study to describe the clinical phenotypes of Chinese DM-MDA5⁺ patients. The delineation of significant characteristic features of different groups provides an important tool to determine the classification and prognosis based on clinical manifestations in daily practice.

In conclusion, DM-MDA5⁺patients have a high mortality rate caused by ILD/RPILD. After analysis of laboratory and clinical features, we divided these patients to 3 phenotypes. Patients aged over 55 years and/or with high level of serum ferritin usually have poor prognosis.

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