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ARTICLE

Different phenotypes in dermatomyositis associated with anti-MDA5 antibody

Study of 121 cases

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Abstract

Objectives

The predominance of extramuscular manifestations (e.g., skin rash, arthralgia, interstitial lung disease [ILD]) as well as the low frequency of muscle signs in anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) dermatomyositis caused us to question the term myositis-specific antibody for the anti-MDA5 antibody, as well as the homogeneity of the disease.

Methods

To characterize the anti-MDA5+ phenotype, an unsupervised analysis was performed on anti-MDA5+ patients (n = 83/121) and compared to a group of patients with myositis without anti-MDA5 antibody (anti-MDA5−; n = 190/201) based on selected variables, collected retrospectively, without any missing data.

Results

Within anti-MDA5+ patients (n = 83), 3 subgroups were identified. One group (18.1%) corresponded to patients with a rapidly progressive ILD (93.3%; $p < 0.0001$ across all) and a very high mortality rate. The second subgroup (55.4%) corresponded to patients with pure dermato-rheumatologic symptoms (arthralgia; 82.6%; $p < 0.01$) and a good prognosis. The third corresponded to patients, mainly male (72.7%; $p < 0.0001$), with severe skin vasculopathy, frequent signs of myositis (proximal weakness: 68.2%; $p < 0.0001$), and an intermediate prognosis. Raynaud phenomenon, arthralgia/arthritis, and sex permit the cluster appurtenance (83.3% correct estimation). Nevertheless, an unsupervised analysis confirmed that anti-MDA5 antibody delineates an independent group of patients (e.g., dermatomyositis skin rash, skin ulcers, calcinosis, mechanic's hands, ILD, arthralgia/arthritis, and high mortality rate) distinct from anti-MDA5− patients with myositis.

Conclusion

Anti-MDA5+ patients have a systemic syndrome distinct from other patients with myositis. Three subgroups with different prognosis exist.

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Glossary

CK = creatine kinase; **DM** = dermatomyositis; **ENMC** = European NeuroMusclar Center; **ICU** = intensive care unit; **ILD** = interstitial lung disease; **MDA5** = melanoma differentiation-associated gene 5; **RP-ILD** = rapidly progressive interstitial lung disease.

Dermatomyositis (DM) is a heterogeneous group of autoimmune diseases, including disorders limited to the skin of patients, with extracutaneous manifestations, such as muscle, articular or pulmonary lesions, and sometimes with an association with malignancy.[1] Myositis-specific autoantibodies permit the delineation of homogenous subgroups of DM.[1,2] DM associated with anti–melanoma differentiation-associated gene 5 antibody (anti-MDA5+) is typically characterized by the presence of a DM skin rash and polyarthralgia and interstitial lung disease (ILD), whereas the clinical signs of myositis are frequently absent.[1,3–5] Anti-MDA5+ DM has a high mortality rate related to the presence of rapidly progressive ILD (RP-ILD).[1]

The predominance and the variety of the extramuscular manifestations, as well as the absence of muscle symptoms, calls into question the term myositis-specific antibody for anti-MDA5 antibodies.

The anti-MDA5 antibody was identified in 2009,[5] and a limited number of case reports and case series have been reported. Knowledge of the precise clinical phenotype and the prognosis of anti-MDA5+ patients is necessary to improve the management of this potentially severe disease.

To characterize the anti-MDA5+ phenotype, we analyzed the characteristics of a large group of patients (n = 121) and performed unsupervised analysis to detect subgroups with different prognoses among anti-MDA5+ patients. We also compared anti-MDA5+ patients with a group of myositis patients without anti-MDA5 antibody (anti-MDA5−; n = 201) to confirm the specificity of the phenotype.

Methods

Patients

Anti-MDA5+ patients were included in the study if they presented any of the following or a combination thereof: a DM skin rash compatible with DM, according to the European NeuroMusclar Center (ENMC) criteria[6] or Sontheimer criteria[7]; myositis (pathologic features showing the presence of inflammatory infiltrates); arthralgia; or ILD, without other etiology. Anti-MDA5 antibody detection was performed using line-immunoassays (Euroimmun [Germany] or D-Tek [Belgium]). This multicenter observational study was performed on data available from 37 medical centers in France from 2011 to 2017. Medical records were reviewed retrospectively (Y.A., S.T., G.L., and Y.U.) to collect clinical, laboratory, and imaging data. ILD was defined based on CT imaging studies and RP-ILD was defined by the acute onset and rapid worsening within 3 months of the onset of respiratory symptoms leading to severe hypoxia ≤60 mm Hg. Early mortality was defined by death within 3 months of the diagnosis. As a control, a cohort of anti-MDA5− patients with myositis was used. All of the controls had myositis defined based on ENMC[6] or Bohan and Peter criteria[8] and were followed in one center (Pitié-Salpêtrière Hospital). The controls' characteristics are detailed in table e-1 (doi.org/10.5061/dryad.t39c4k1).

Standard protocol approvals, registrations, and patient consents

Agreement for the study was obtained from the French Ministry of Research (CCTIRS no. 14.323 and AC-2013-1868) and the study was approved by the Research Ethics Committee of the Pitié-Salpêtrière Hospital (Paris, France).

Statistics

Quantitative data (median [interquartile range]) and qualitative data (frequency and percentage) were described. Unsupervised descriptive methods of statistical learning were used to analyze either the anti-MDA5+ patients or the global cohort of patients with myositis (anti-MDA5+ and anti-MDA5−). A multiple correspondence analysis and hierarchical cluster analysis were used to resume the dataset and aggregate patients in subgroups, as previously reported.[9] Only patients with an exhaustive set of data were included for the unsupervised analysis. The clustering of patients was unsupervised using Euclidean distance and the Ward agglomerative method. V test p values are represented for the variables that participated in the multidimensional analyses (see supplemental tables, doi.org/10.5061/dryad.t39c4k1).[10] In addition, the Wilcoxon test was used to compare quantitative data and anti-MDA5 status (positive or negative), and Fisher exact test was used for qualitative data in the different groups (anti-MDA5 status [positive or negative]) or global association with the clusters obtained by hierarchical cluster analysis (tables 1 and 2).

To construct a decisional algorithm tree to position the patients in a cluster, we used classification and regression trees. A p value <0.05 was considered significant. For the survival analysis, Kaplan-Meier curves were performed on different patient subgroups and compared using log-rank tests. Statistical analyses were performed (R version 3.4.0 software and GraphPad Prism software).

Data availability

All supplementary data are available from the Dryad digital repository (doi.org/10.5061/dryad.t39c4k1). Further anonymized

Table 1 Characteristics of 3 groups of anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) patients

	Cluster 1 (n = 15)	Cluster 2 (n = 46)	Cluster 3 (n = 22)	*p* Value
Sex[a]				
Women	11 (73.3)	38 (82.6)	6 (27.3)	<0.0001
Men	4 (26.7)	8 (17.4)	16 (72.7)	
Ethnicity[a]				
Caucasian	6 (40)	23 (50)	12 (54.5)	0.67
African	7 (46.7)	20 (43.5)	10 (45.4)	
Asian	2 (13.3)	2 (4.5)	0 (0)	
Hispanic	0 (0)	1 (2.2)	0 (0)	
General condition/inflammation				
Fever	6 (40)	14 (30.4)	9 (42.9)	0.57
Deterioration of general condition[a]	14 (93.3)	30 (65.2)	10 (45.4)	0.008
CRP or ESR increase	7 (58.3)	18 (41.9)	9 (47.4)	0.62
Skin changes				
Skin lesions[a]	15 (100)	38 (82.6)	21 (95.4)	0.16
Mechanic's hands[a]	11 (73.3)	20 (43.5)	3 (13.6)	0.0011
Typical DM skin rash[a]	12 (80)	31 (67.4)	17 (77.3)	0.63
Raynaud phenomenon[a]	1 (6.7)	5 (10.9)[a]	18 (81.8)	<0.0001
Skin ulcers[a]	4 (26.7)	17 (37)	17 (77.3)	0.002
Digital necrosis[a]	0 (0)	2 (4.3)	7 (31.8)	0.002
Calcinosis[a]	0 (0)	2 (4.3)	5 (22.7)	0.02
Skin sclerosis[a]	1 (6.7)	2 (4.3)	5 (22.7)	0.05
Muscular manifestations				
Proximal weakness[a]	4 (26.7)	7 (15.2)[a]	15 (68.2)	0.0001
MRC ≤3[a]	0 (0)	1 (2.3)	5 (26.3)	0.003
Increased CK level[a]	10 (66.7)	10 (21.7)	14 (63.6)	0.0004
CK >160 IU/L and <800 IU/L[a]	10 (66.7)	11 (24)	6 (27.3)	
>800 IU/L[a]	1 (6.7)	0 (0)	8 (36.4)	
Myositis on muscle biopsy	2 (50)	12 (52.2)	9 (56.2)	1
Lung manifestations				
Dyspnea[a]	15 (100)	28 (60.9)	10 (45.4)	0.0008
ILD[a]	15 (100)	38 (82.6)	11 (50)	0.0008
RP-ILD[a]	14 (93.3)	8 (17.4)	5 (22.7)	<0.0001
PaO_2 <60 mm Hg	13 (92.8)	8 (23.6)	8 (57.1)	<0.0001
Rheumatologic manifestations				
Arthritis/arthralgia[a]	4 (26.7)	38 (82.6)	17 (77.3)	0.0003
Synovitis[a]	1 (6.7)	17 (37)	9 (41)	0.0479
RF or anti-CCP antibody	3 (27.7)	5 (13.5)	4 (21)	0.46

Continued

Table 1 Characteristics of 3 groups of anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) patients *(continued)*

	Cluster 1 (n = 15)	Cluster 2 (n = 46)	Cluster 3 (n = 22)	*p* Value
Outcomes				
ICU[a]	13 (86.7)	5 (10.9)[a]	8 (36.4)	<0.0001
Death within 3 months[a]	12 (80)	0 (0)[a]	1 (4.5)	<0.0001
Miscellaneous				
Malignancy[a]	1 (6.7)	2 (4.3)	1 (4.5)	1
Lymphadenopathy	5 (38.5)	15 (33.3)	4 (19)	0.4
Seritis	0 (0)	7 (16.7)	4 (18.2)	0.27
Increased liver enzymes	8 (66.7)	16 (40)	11 (61.1)	0.18
Leukopenia	2 (16.7)	13 (31.7)	3 (15)	0.32
ANA	5 (41.7)	21 (55.3)	11 (57.9)	0.72

Abbreviations: ANA = antinuclear antibody; anti-CCP = anti–cyclic citrullinated peptide antibody; CK = creatine kinase; CRP = C-reactive protein; DM = dermatomyositis; ESR = erythrocyte sedimentation rate; ICU = intensive care unit; ILD = interstitial lung disease; MRC = Medical Research Council scale; RF = rheumatoid factor; RP-ILD = rapidly progressive interstitial lung disease.
Values are n (%).
[a] Variables used in the unsupervised analysis permitting us to identify the 3 clusters. The other variables (not used for the clustering, because not available for all anti-MDA5+ patients) were positioned in the different clusters.

data can be made available to qualified investigators upon request to the corresponding author.

Results

Three MDA5+ patient subgroups

Anti-MDA5+ patients (n = 121) were mainly female, 49 years old (34–58), and Caucasian, but African origin was also frequent. As expected, most of the patients had a DM skin rash (71.2%), ILD (76.5%), and arthralgia (69%), whereas only one-third of patients had muscle weakness (table e-2, doi.org/10.5061/dryad.t39c4k1). Of note, 2 patients had concomitant myocarditis with severe cardiac failure.

We aimed to identify the phenotype variations within the anti-MDA5+ group (n = 83/121). The unsupervised hierarchical analysis tree that we positioned on the factorial map showed 3 clusters (figure 1, A and B). The characteristics of each cluster are reported in table 1.

Cluster 1 (18.1%; n = 15) corresponded to patients with very severe lung disease (RP-ILD cluster). All patients had ILD, and all but one had RP-ILD (93.3%; V test $p < 0.0001$). Patients in this cluster were admitted to the intensive care unit (ICU) in 86.7% of cases ($p < 0.0001$). The early mortality rate was high (80%; V test $p < 0.0001$). The other main characteristic was that these patients frequently had mechanic's hands (73.3%; V test $p = 0.006$).

Cluster 2 (55.4%; n = 46) corresponds to a pure dermato-rheumatologic pattern (rheumatoid cluster). As for the RP-ILD cluster, patients in cluster 2 were mainly women and less frequently had skin lesions (82.6%; V test $p = 0.03$), digital necrosis (4.35%; $p = 0.04$), and the Raynaud phenomenon (10.9%; V test $p < 0.0001$) (table 1). Most patients in cluster 2 complained of arthralgia or arthritis (82.6%; V test $p = 0.01$). Signs of myositis (muscle weakness 15.2%; V test $p = 0.0005$ and increased creatine kinase [CK] level 21.7%; V test $p < 0.0001$), as well as RP-ILD (17.4%; V test $p = 0.001$), were infrequent, and no early death occurred in this group (V test $p < 0.0001$).

Cluster 3 (26.5%; n = 22) corresponded to patients with severe skin vasculopathy and an intermediate prognosis (vasculopathic cluster). Patients here were mainly male (72.7%; V test $p < 0.0001$). In addition to the classical DM skin rash, those patients frequently harbored signs of skin vasculopathy with the Raynaud phenomenon (81.8%; V test $p < 0.0001$), skin ulcers (77.3%; V test $p = 0.0006$), digital necrosis (31.8%; $p = 0.001$), and calcinosis (22.7%; V test $p = 0.01$). In addition, most patients had proximal weakness (68.2%; V test $p < 0.0001$) with increased CK levels in 63.6% (V test; $p < 0.0001$). Some of the patients in cluster 3 had RP-ILD (22.7%), and the early mortality rate was low (4.5% in the vasculopathic cluster).

Three different MDA5+ patients prognoses

We next analyzed the long-term survival of anti-MDA5+ patients depending on the 3 clusters (figure 2A). The analysis clearly confirmed a different prognosis between the clusters. The RP-ILD cluster had a very high mortality rate compared to patients in the rheumatic and vasculopathic clusters ($p <$

Table 2 Comparison of anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) vs anti-MDA5− patients with myositis

	Anti-MDA5− (n = 201)	Anti-MDA5+ (n = 121)	*p* Value
Sex			
Male	56 (27.9)	40 (33.1)	0.3889
Ethnicity			
Caucasian	144 (71.6)	56 (48.3)	<0.0001
African	30 (14.9)	50 (43.1)	
Asian	6 (3)	8 (6.9)	
Others	21 (10.4)	2 (1.7)	
Skin			
Skin lesions	129 (64.2)	105 (87.5)	<0.0001
Typical DM skin rash	54 (26.9)	84 (70)	<0.0001
Mechanic's hands	35 (17.4)	50 (42.7)	<0.0001
Raynaud phenomenon	70 (35.2)	34 (29.8)	0.3995
Skin ulcers	11 (5.5)	49 (41.5)	<0.0001
Calcinosis	4 (2)	12 (10.2)	0.003
Muscle			
Proximal weakness	180 (90)	35 (30.7)	<0.0001
Psoas MRC ≤3	107 (57.53)	8 (8.2)	<0.0001
Increased CK level	190 (94.5)	46 (41.4)	<0.0001
CK level >800 IU/L	162 (80.6)	13 (10.7)	<0.0001
Myositis on biopsy	170 (90.9)	30 (55.6)	<0.0001
Joints			
Arthritis/arthralgia	92 (45.8)	80 (69)	<0.0001
Lungs			
Dyspnea	137 (70.3)	80 (66.7)	0.5871
ILD	90 (46.4)	91 (76.5)	<0.0001
Malignancy	24 (12)	9 (7.6)	0.296
Death	13 (6.8)	33 (27.3)	<0.0001

Abbreviations: CK = creatine kinase; DM = dermatomyositis; ILD = interstitial lung disease; MRC = Medical Research Council scale.
Values are n (%).

0.0001). Comparing patients in the rheumatic cluster to those in the vasculopathic cluster, it appeared that the prognosis was better (very good) in the rheumatic cluster than in the vasculopathic cluster ($p = 0.01$).

Finally, we aimed to easily position a participant in one of the 3 clusters. Classification and regression tree analysis was used as a predictive model to determine the items permitting us to classify a patient (figure 2B). Because we aimed to predict patient outcome, the variables related to obvious severity were removed (RP-ILD and ICU). The models including 3 variables Raynaud phenomenon, arthralgia/arthritis, and sex permits 83.3% correct estimation. Of note, adding the variable RP-ILD permits us to reach 91.6% correct estimation.

Comparison of anti-MDA5+ vs anti-MDA5− patients

Because we observed the different subgroups of anti-MDA5+ patients, we aimed to verify if anti-MDA5+ disease remains a separate entity within myositis. We compared anti-MDA5+ patients (n = 121) to anti-MDA5− myositis patients (n = 201) (table 2).

Compared to anti-MDA5− patients, anti-MDA5+ patients were more frequently African, more frequently had a DM skin rash, skin ulcers, calcinosis, mechanic's hands, ILD, and arthralgia/arthritis, and had a higher mortality rate (table 2). Anti-MDA5− patients had more severe myositis (based on muscle weakness and CK level).

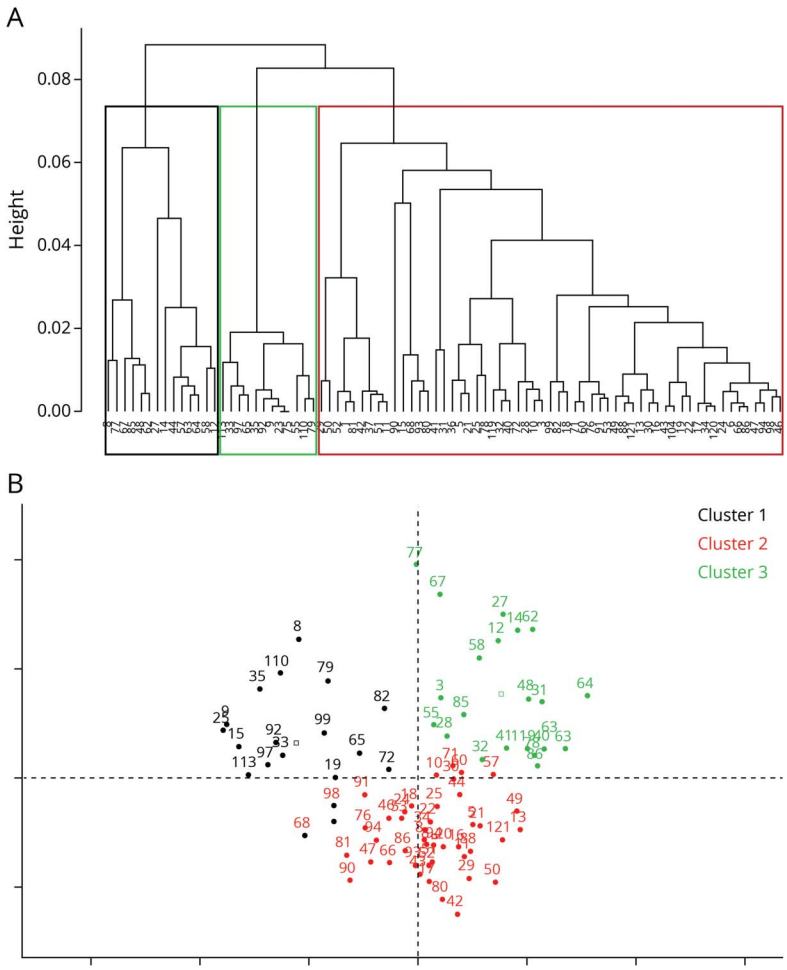
Next, we performed an unsupervised hierarchical clustering analysis in a large group of patients with myositis (anti-MDA5+ and anti-MDA5− patients; n = 274/322) with 20 variables, including long-term mortality (table e-2, doi.org/10.5061/dryad.t39c4k1), but importantly not including anti-MDA5 antibody status. We clearly observed 2 clusters (figure 3 and figure e-1, doi.org/10.5061/dryad.t39c4k1). The hierarchical tree positioned on the factorial map showed that cluster 2 regrouped mainly anti-MDA5+ patients (87.5%; n = 84/96 vs 7.3%; n = 13/178; $p < 0.0001$) after having positioned the variable anti-MDA5. The anti-MDA5 antibody delineates an independent subgroup of patients from a large cohort of patients with myositis.

Discussion

We report the phenotype of a large group of anti-MDA5+ patients. Overall, our observation confirmed previous studies showing that anti-MDA5+ patients present a DM skin rash with frequent signs of skin vasculopathy,[3] frequent arthralgia/arthritis,[4] and ILD with a high mortality rate.[1]

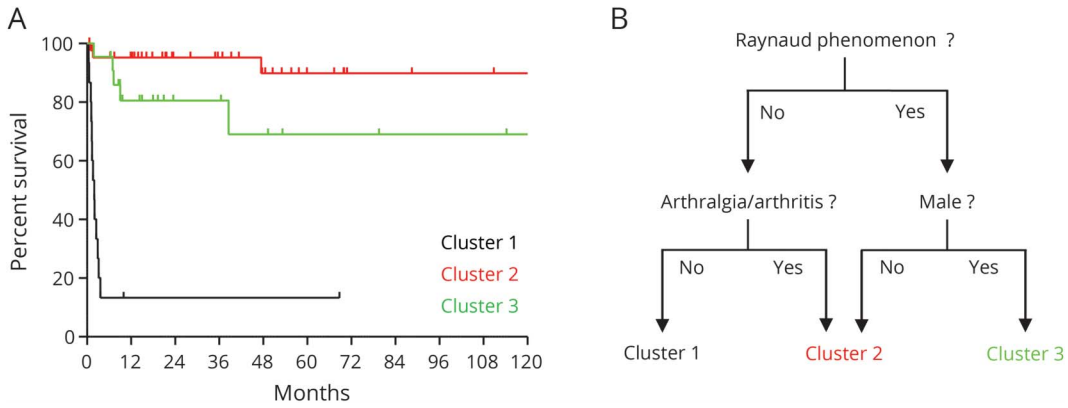
Using unsupervised analyses, we observed for the first time 3 distinct subgroups with different prognoses. The RP-ILD cluster with severe lung involvement and a poor prognosis corresponds to well-recognized anti-MDA5+ RP-ILD.[1,5] In addition, we were able to isolate 2 new forms: anti-MDA5+ rheumatic DM, with a good prognosis, and anti-MDA5+ vasculopathic DM, with an intermediate prognosis. The algorithm decisional algorithm showed that only 3 variables (Raynaud phenomenon, arthralgia/arthritis, and sex) are good predictors for cluster appurtenance.

Figure 1 Unsupervised analysis of anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) patients



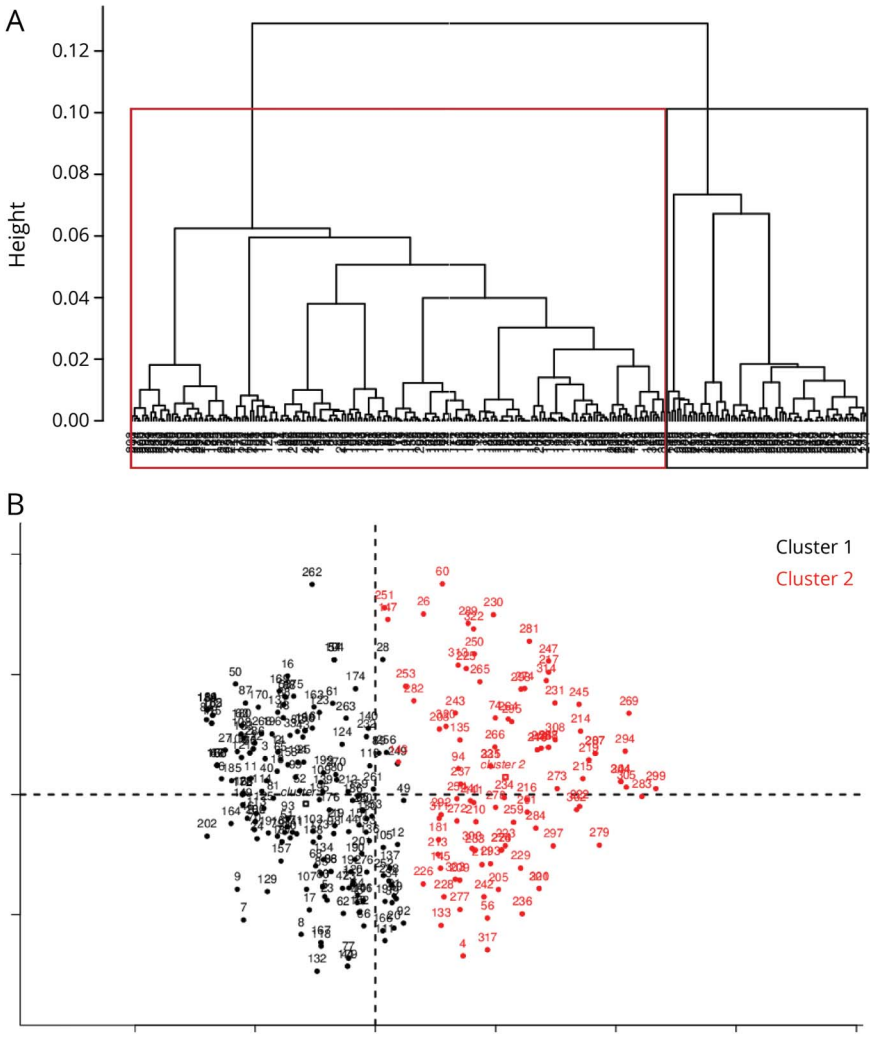
(A) The hierarchical cluster analysis of anti-MDA5+ patients showed 3 clusters (the variables included in the unsupervised analysis were sex, ethnicity, skin changes, typical dermatomyositis skin rash, mechanic's hands, skin ulcers, calcinosis, digital necrosis, sclerosis, Raynaud phenomenon, abnormal creatine kinase [CK] level, CK level, proximal muscle weakness, manual muscle testing score of the psoas [Medical Research Council score], arthritis/arthralgia, synovitis, dyspnea, interstitial lung disease [ILD], rapidly progressive ILD, resuscitation, deterioration of general status, malignancy, intensive care unit admission, malignancy within 3 years before or after the myositis diagnosis, and early mortality). (B) Multiple correspondence analysis confirmed the presence of 3 groups of anti-MDA5+ patients. All above-mentioned variables except intensive rapidly progressive ILD, care unit admission, and mortality were included in the classification algorithm regression tree analysis.

Figure 2 Anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) prognosis



(A) The survival curves showed that cluster 1 (black) had a poor prognosis, cluster 2 (red) had a good prognosis, and cluster 3 (green) had a mild prognosis. (B) Pruned model of prediction without obvious signs of severity (the variables included in the classification algorithm regression tree analysis did not encompass obvious signs of severity [rapidly progressive interstitial lung disease (ILD), intensive care unit admission, and mortality], sex, ethnicity, skin changes, typical dermatomyositis skin rash, mechanic's hands, skin ulcers, calcinosis, digital necrosis, sclerosis, Raynaud phenomenon, abnormal creatine kinase [CK] level, CK level, proximal muscle weakness, manual muscle testing score of the psoas [Medical Research Council score], arthritis/arthralgia, synovitis, dyspnea, ILD, deterioration of the general status, malignancy, and malignancy within 3 years before or after the myositis diagnosis).

Figure 3 Unsupervised analysis of anti–melanoma differentiation-associated gene 5 antibody–positive (anti-MDA5+) and anti-MDA5− patients



(A) Hierarchical cluster analysis of anti-MDA5+ patients and anti-MDA5− myositis patients without including the anti-MDA5 antibody status as variable (the variables included for the unsupervised analysis were sex, ethnicity, proximal muscle weakness, abnormal creatine kinase [CK] level, CK level, skin changes, typical dermatomyositis skin rash, mechanic's hands, skin ulcers, calcinosis, Raynaud phenomenon, arthritis/arthralgia, dyspnea, interstitial lung disease, and malignancy within 3 years before or after the myositis diagnosis). The analysis permitted the identification 2 main clusters. (B) Using multiple correspondence analysis, both clusters were positioned on the factor map of individuals, which confirmed that patients were segregated into 2 groups. When the variable anti-MDA5 was next positioned, it appeared that cluster 2 was mainly composed of anti-MDA5+ patients (87.1%).

These observations and the large spectrum of disease manifestations suggest that the so-called anti-MDA5+ DM is rather a systemic syndrome (anti-MDA5+ syndrome) than a musculocutaneous disease.

This finding underlines the importance of anti-MDA5 antibody screening in patients with seronegative polyarthritis and patients with interstitial pneumonia, with a suspicion of autoimmune features,[11] or ICU patients with acute respiratory distress syndrome of unknown origin. The prognosis related to the different clusters is also important regarding the treatment strategy and may suggest different pathophysiologic mechanisms.

The comparison of anti-MDA5+ patients with a large cohort of MDA5− patients showed that anti-MDA5+ syndrome remains a separate entity. Using unsupervised clustering analysis, we showed that the anti-MDA5+ antibody was independently and strongly associated with this phenotype. This result emphasizes the crucial role of myositis-specific antibodies to diagnose and delineate a subgroup of patients. However, the term myositis-specific antibody seems inappropriate, because many anti-MDA5+ patients are amyopathic.

The nationwide retrospective cohort study design we used is the main limitation of our work. The low frequency of the reported rheumatologic signs in the RP-ILD cluster could be due to a detection bias since the majority of patients were in the ICU. Nevertheless, patients in the RP-ILD cluster were also characterized by an increased CK level, whereas this was not the case for patients with the rheumatologic form in cluster 2.

Together, these data show that anti-MDA5+ patients are a distinct group from patients with myositis and have a systemic syndrome composed of 3 different entities with different prognoses. The anti-MDA5+ antibody is a key biomarker to define this syndrome.

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Ségolène Toquet, MD	Sorbonne Université, Paris	Major role in data acquisition, revised the manuscript for intellectual content
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Benjamin Grange, MD	Sorbonne Université, Paris	Interpreted the data and statistical analysis
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Appendix *(continued)*

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Different phenotypes in dermatomyositis associated with anti-MDA5 antibody: Study of 121 cases

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