Predictive factors of anti-MDA5 antibody in patients with dermatomyositis: a retrospective multicenter study

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Abstract

Background and objectives: Melanoma differentiation-associated gene 5 antibody (anti-MDA5) in dermatomyositis (DM) has been associated with rapidly progressive interstitial lung disease and poor prognosis. Early diagnosis is key to improving the prognosis of these patients. The aim was to confirm cutaneous characteristics in patients with anti-MDA5 dermatomyositis and explore new diagnostic markers of anti-MDA5 presence (anti-MDA5$^+$).

Patients and Methods: Multicenter cross-sectional retrospective cohort study of 124 patients diagnosed with DM, 37 of them were anti-MDA5$^+$. Demographic, laboratory data and clinical manifestations were collected.

Results: Anti-MDA5$^+$ DM is characterized by a particular mucocutaneous phenotype that includes oral lesions, alopecia, mechanic's hands, palmar and dorsal papules, palmar erythema, vasculopathy and skin ulceration. We found vasculopathy and digital tip involvement very frequent in anti-MDA5$^+$ patients ($P < 0.001$), being a diagnostic marker of anti-MDA5$^+$ (OR, 12.355; 95%CI 2.850-79.263; $P = 0.012$ and OR, 7.447; 95%CI 2.103–46.718; $P = 0.004$ respectively). The presence of ulcers requires a special mention, especially in anti-MDA5$^+$ patients, because in our cohort, up to 97% of the anti-MDA5$^+$ patients had ulcers.

Conclusions: In patients with suspected DM with digital tip involvement or vasculopathy, the presence of anti-MDA5 antibodies must be ruled out, as it may be a clinical predictor.

Keywords: dermatomyositis; anti-MDA5; ulcers; vasculopathy; arthritis.

Introduction

Different antibodies specific to dermatomyositis (DM) have been described. Among these is an antibody directed against the protein encoded by melanoma differentiation-associated gene-5 antibody (anti-MDA5), which was discovered in 2005.[1] The presence of anti-MDA5 in patients with DM has been associated with severe pulmonary involvement in a high number of cases, with a 5-year survival rate of 56%.[2] Therefore, early diagnosis is key to improving the prognosis of these patients.[3,4] In this sense, it is essential to know the cutaneous manifestations that should allow us to suspect the presence of this antibody. Although specific clinical characteristics associated with anti-MDA5, such as painful palmar papules or panniculitis, have been described, the spectrum of manifestations it encompasses is still not well understood.[5,6] On the other hand, it has also been observed that in this specific type of DM, ferritin levels and erythrocytes sedimentation rate (ESR) are usually high, and there may be lymphopenia,[5,7] however, the available data regarding other laboratory parameters are insufficient.

We hypothesize that anti-MDA5 in DM is associated with rapidly progressive interstitial lung disease and poor prognosis. Therefore, the aims of our study were to confirm previously described cutaneous characteristics in patients with anti-MDA5 dermatomyositis and explore possible new clinical (with emphasis on cutaneous) and laboratory manifestations that can predict the presence of this antibody, enabling the dermatologist to suspect this disease early.

Materials and Methods

Study design and patients

Multicenter cross-sectional retrospective cohort study was carried out in patients diagnosed with DM at 21 Spanish hospitals in the National Health System, which contributed all the cases that were registered. The inclusion criteria were: patients with ≥18 years old with a diagnosis of DM confirmed by the Dermatology and Rheumatology services according to

the criteria described by Bohan and Peter.[8] It was not mandatory to have a skin or muscle biopsy to be included in the study. All patients had to be tested for the detection of IgG antibodies against Jo-1, PL-7, PL-12, EJ, SRP, Mi-2, MDA-5, TIF1-γ, SSA / Ro52kD, SAE1, SAE2 and NXP-2 antigens.

An a priori sample size calculation indicated that 120 participants were needed to obtain statistically significant differences in predictor variables with anti-MDA5^{+} respect to anti-MDA5^{-} in patients with DM. With $\alpha = 0.05$, $\beta = 0.8$, and utilizing a between participant comparison (to be conservative given any unknown patients differences with this methodology), n = 108 participants were determined to be sufficient to detect a significant difference between anti-MDA5^{+} and anti-MDA5^{-}, according to Shakshouk et al.[9] To account for a potential 20% drop out rate, we recruited n = 124 participants. The required sample size was determined using G*Power software.[10]

Patients whose diagnosis was in doubt or who had a disease with manifestations that may be similar (such as lupus erythematosus or photosensitive diseases) were excluded from the study. The diagnosis of interstitial lung disease was established with high-resolution computed tomography (CT), and rapidly progressive interstitial lung disease (RP-ILD) was defined as radiological worsening with progression of dyspnea and hypoxemia in the month following the diagnosis of lung disease. A positive antinuclear antibody (ANA) was defined as reactivity at greater than 1:80 titer using Hep2 cells. Crithidia luciliae kinetoplast assay was applied for dsDNA testing

Patients agreed to participate in the study by signing the written informed consent form. The study protocol was approved by the Ethics Committee for Drug Research of the Hospital Universitario de La Paz (PI-4305) and complied with the Declaration of Helsinki of 1964 (last updated 2013).

Data measurement

Demographic and laboratory data, and clinical manifestations (systemic and cutaneous), were collected retrospectively in a digital form from the patients' medical records from June to October 2020.

A qualitative Enzyme Immunoassay was used to detect IgG antibodies against Jo-1, PL-7, PL-12, EJ, SRP, Mi-2, MDA-5, TIF1-γ, SSA / Ro52kD, SAE1, SAE2 and NXP-2 antigens according to manufacturer's instructions.

Statistical analysis

Quantitative data (median [interquartile range]) and qualitative data (frequency and percentage) were described. Unsupervised descriptive methods of statistical learning were used to analyze anti-MDA5^{+} patients and the global cohort of patients with myositis (anti-MDA5^{+} and anti-MDA5^{-}).

We compared the clinical features of complementary patients with and without anti-MDA5, using Student's t test for continuous variables and two-tailed Fisher's exact test for categorical variables. Multivariable analysis using adjusted Odds Ratio (OR) with 95% confidence interval (95% CI) analysis was performed for positive (OR >1) or negative prediction (OR <1) of DM using variables with $P < 0.100$ in the univariable analyses).

Statistical significance was set at $P < 0.05$.

Results

Data was collected from 124 patients with DM diagnosed during dermatology consultations at 21 Spanish hospitals. The mean age at diagnosis was 55.2 years and most patients were Caucasian (83.9%) and women (79%). The characteristics of patients are shown in Table 1.

Anti-MDA5 antibodies were detected in 37 (29.8%) patients and absent in 87 (70.2%) patients (Table 1). Of the anti-MDA5^{+} patients, 10, 5, and 1 were found to have antibodies to Ro-52, Anti-Ro/SSA or SAE antibodies, and TIF-1 gamma, KU, or PL-7 antibodies,

respectively, whereas none had reactivity to Jo-1, Mi-2 or NXP2. These results were confirmed with a different laboratory technique.

The anti-MDA5 phenotype

The characteristics and comparison of patients with anti-MDA5^{+} and anti-MDA5^{-} DM are shown in Table 2.

A univariate prediction analysis was performed among anti-MDA5^{+} patients. The variables with $P < 0.100$ were included in the multivariate analysis with adjusted OR was performed to identify predictive variables for anti-MDA5^{+}. The variables included were age, oral lesions, alopecia, diffuse alopecia, mechanic's hands, muscle weakness, severe muscle weakness, arthritis, peripheral and acral arthritis, pulmonary involvement, interstitial pneumonitis, altered pulmonary function testing, palmar papules, dorsal papules, palmar erythema, skin ulceration, acral ulceration, limb root ulceration (groins and armpits), elevated liver enzymes, vasculopathy, elevated ferritin, elevated creatin phosphokinase (CPK), elevated VSG, lymphopenia, race, digital tip involvement, anti TIF-1 gamma, anti Jo-1, anti Mi-2 and Hyperkeratosis. Of all the variables described, the following were associated with the presence of anti-MDA 5: vasculopathy ($P = 0.012$) , arthritis ($P = 0.015$), digital tip involvement ($P = 0.004$), elevated ferritin ($P = 0.013$) and pulmonary involvement ($P = 0.034$). On the other hand, it was obtained a negative prediction regarding muscle weakness ($P = 0.006$) and anti TIF-1 gamma ($P = 0.011$) (Table 3).

There was no statistically significant relationship between pulmonary involvement in general and the presence of anti-Ro52 antibody, but a trend was observed, with 14.6% of anti-Ro52^{+} patients having no lung involvement compared to 28.6% with lung involvement OR 2.343(95% CI, 0.865-6.34; $P = 0.088$). Likewise, no statistically significant differences were found between RP-ILD and the presence of anti-Ro52 antibody. Of the anti-Ro52^{+} patients, 17.4% did not show signs of RP-ILD, while 33.3% were diagnosed with RP-ILD OR 2.381

(95% CI, 0.206-27.485; *P* = 0.474). In addition, no statistically significant differences were observed between anti-Ro52 and lung involvement, particularly in patients with anti-MDA5^{+} (37 patients) OR 1.875 (95% CI, 0.429-8.199; *P* = 0.407).

Discussion

In view of our results and from a dermatological point of view, in patients with suspected DM with digital tip involvement (macules, papules, ulcers, necrosis, erythema), or vasculopathy, the presence of anti-MDA5 antibodies must be ruled out, as it is a clinical predictor (Figures 1 and 2).

In addition, anti-MDA5^{+} patients present more frequently with palmar and dorsal papules; palmar erythema; skin ulcers, especially at the acral level or on the roots of the limbs (groins and armpits); diffuse alopecia; oral lesions; and/or mechanic's hands (Figures 3 and 4). Also, the presence of arthritis, with little muscle involvement and distinct hyperferritinemia in the complementary study, most likely indicates anti-MDA5 DM.

To date, most publications regarding anti-MDA5^{+} DM consist of case series or isolated cases. There are few studies involving anti-MDA5^{+} patients, our study being the one with the highest number of total cases. Other than the present study, only one study was a multicenter study.[9,11-14]

Extracutaneous manifestations

Currently, anti-MDA5 is considered a biomarker of (in some cases, very severe) pulmonary involvement, polyarthralgia, and usually little muscle involvement in carrier patients, which is in line with what our data reflects (Table 2).[12] In our sample, almost half (48.6%) of the patients had lung involvement, of which 5.4% developed RP-ILD. These lung involvement rates are significantly lower than those found in other studies.[13,15] This can be explained by the fact that most previous studies related to the presence of anti-MDA5 evaluated lung disease as the main manifestation. To date, it is known that not all patients with

this antibody have the same pulmonary involvement or the same prognosis, and diagnosis based on suspected non-pulmonary manifestations has increased. Similarly, muscle involvement is greater in the group of patients anti-MDA5$^-$ (77% vs 48.6%; $P < 0.001$).

Anti-MDA5 antibodies have been reported in patients with symmetric polyarthritis like rheumatoid arthritis. These patients often show features of anti-synthetase syndrome but without specific antibodies.[8] In agreement with these findings, 37.8% of the anti-MDA5$^+$ patients vs in 16.1% of the anti-MDA5$^-$ patients ($P < 0.001$) in our study developed arthritis; however, we emphasize the peripheral and acral involvement. In our cohort, patients anti-MDA5$^+$ did not have antisynthetase syndrome more frequently than anti-MDA5$^-$ ($P = 0.353$).

The link between dermatomyositis and cancer is well known and some antibodies are considered markers because their association with cancer is particularly high, such as anti-transcriptional intermediary factor (TIF)1-γ antibody. However, it is interesting to corroborate that the presence of anti-MDA5 antibody did not seem to lead to an increase in the appearance of neoplasms, as has been previously published.[5,12,13,16] In fact, the percentage of patients with neoplasia was similar in both groups in the present cohort of patients.

Cutaneous manifestations

In view of what has been previously published and, in line with our analysis, anti-MDA5$^+$ patients do not usually show the classical clinical symptoms of DM. For example, heliotrope rash, Gottron's papules, and the typical involvement of the V neckline are not observed more frequently.[12,13] However, it is noteworthy that other authors, such as Huang et al., have found them in up to 100% of patients.[5,17]

Shakshouk et al.[9] also found Gottron papules on hands and Gottron sign on elbows as the most common dermatologic finding in their patients in a recently publication.

The authors wish to highlight the frequency of acral lesions (mainly on the hands) present in these patients. On the one hand, the well-known palmar papules (somewhat less dorsal)[5] were present in almost half of our patients, as in the Fiorentino et al.[12] study.

However, our multivariate analysis did not demonstrate their ability to predict the presence of anti-MDA5.

On the other hand, we found that in addition to digital tip involvement being frequent in anti-MDA5$^+$ patients (37.8% of cases; $P < 0.001$), this manifestation is a diagnostic marker of anti-MDA5 presence (OR, 7.447; 95% CI, 2.103–46.718; $P = 0.004$) (Table 3). To date, several authors have described the presence of ulcers on the digital tip, but in isolated cases.[14,18] In addition to ulcers, we included erythema, macules, papules, ulcers, and necrosis.

Recently, ulceration of the thumbs has been described in three patients with dermatomyositis and calcinosis cutis. They also highlight the presence of ulcers on this location as a frequent manifestation in these patients.[9]

Finally, palmar erythema (present in up to 48.5% of patients [$P < 0.001$]), mechanic's hands (16.2%; $P = 0.042$), and skin ulceration at other levels, in addition to acral (18.9%; $P < 0.001$) were also found more frequently in anti-MDA5$^+$ patients. These findings highlight the importance of studying the hands of these patients, as they can give a diagnostic key.

Also deserving of special mention is the presence of signs of vasculopathy, especially the presence of ulcers in anti-MDA5$^+$ patients, which has been previously described by other studies who found them in 41.5% of their patients.[6,11,14,19] In our cohort, it is striking that up to 97% of the anti-MDA5$^+$ patients had ulcers, highlighting their presence at the acral level and in groins and armpits as significant data, not published to date.

Finally, in line with previous publications, the presence of oral lesions and alopecia was noted more frequently in patients with anti-MDA5$^+$ DM, although this was less frequent than in other series (37.8% vs almost 80% in other series).[12] However, unlike previous

196 publications, we could not establish a relationship with panniculitis, periungual involvement[12]
197 or calcinosis,[13] but we confirmed that the presence of Raynaud's disease is rare.[5] Interestingly,
198 other authors found highly significant increased frequency of Raynaud syndrome in
199 association with anti-MDA5 seropositivity, not emphasized in the literature to date.[9]

200 **Laboratory data**

201 A higher proportion of elevation of liver enzymes, ESR and hyperferritinemia as well
202 as lymphopenia was found in anti-MDA5$^+$ patients ($P < 0.05$, Table 2), highlighting ferritin as
203 a predictor of the presence of the antibody (OR, 7.143; 95% CI, 1.517-33.654; $P = 0.013$).

204 There are previous studies highlighting the fact that elevated levels of ferritin are
205 related to disease activity.[5,20] In our sample, it was not possible to collect this data. There is
206 only one article that lists lymphopenia as a noteworthy feature in patients with anti-MDA5
207 DM. In the present sample, 40.5% of the anti-MDA5$^+$ patients presented with lymphopenia.
208 We believe that it would be interesting to establish some line of study in this regard in the
209 future.

210 Finally, we wish to highlight that one anti-MDA5$^+$ patient also tested positive for TIF-
211 1 gamma, another for Ku, and a third for PL-7. To date, there are very few reports of patients
212 positive for more than one myositis-specific antibody.[12,17] In fact, a review by Kurtzman and
213 Vleugels revealed that anti-MDA5 antibodies seem to be exclusive of other myositis-specific
214 antibodies.[5]

215 The present study had several limitations. First, as it was a retrospective multicenter
216 study, it was difficult to compare the measurements of anti-MDA-5 and some laboratory
217 variables (such as CPK or ferritin, for example) on arrival from different laboratories. Second,
218 most of our patients were Caucasian, with the rest of the races probably underrepresented.

219 However, as we included all types of patients with anti-MDA5$^+$, regardless of their
220 severity and irrespective of lung involvement, we avoided the biases derived from these

variables. We included controls with the same disease, avoiding possible biases in the comparison with other diseases with similar manifestations.

Conclusions

Patients with anti-MDA5 DM have particular clinical and laboratory characteristics compared to other types of DM. Hand lesions, especially at the digital tip, and evidence of vascular disease are notably frequent. In a patient with lesions in this location, arthritis, and hyperferritinemia, the presence of anti-MDA5 should be investigated to rule out pulmonary involvement.

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Conflict of Interest

None.

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Figure Legends

Figure 1. Erythema, ulcers, and digital tip involvement in a patient with anti-MDA5^{+} dermatomyositis.

Figure 2. Palmar lesions with tip involvement in a patient with anti-melanoma differentiation associated gene 5 antibody positive dermatomyositis.

Figure 3. Painful ulcers on dorsal surface of the hands.

Figure 4. Typical palmar papules in a patient with anti-melanoma differentiation associated anti-MDA5^{+}.

Tables

Table 1. Characteristics of patients.

	N (%)
Gender	
Male	26 (21)
Female	98 (79)
Race	
Caucasian	104 (83.9)
Latino	14 (11.3)
Asian	4 (3.2)
African	2 (1.6)
Mean age at diagnosis, years ± SD	55.2 ± 17.7
Autoantibody status	
ANA	79 (63.7)
MDA-5	37 (29.8)
Ro-52	22 (17.7)
Anti-Ro/SSA	18 (14.5)
TIF-1 gamma	21 (16.9)
Jo-1	9 (7.3)
Mi-2	11 (8.9)
SAE	5 (4)
NXP2	2 (1.6)
KU	2 (1.6)
PL-7	1 (0.8)
Other antibodies	33 (26.6)

Table 2. Comparison of anti-MDA5^{+} vs anti-MDA5^{-} patients with dermatomyositis.

	Total (N = 124), N (%)	anti-MDA5^{+} (N=37), N (%)	anti-MDA5^{-} (N=87), N (%)	*P* value
Age onset, years ± SD	**55.2 ± 17.7**	**49.0 ± 16.0**	**57.8 ± 17.8**	**0.011**
Race				
Caucasian	**104 (90.8)**	**25 (67.6)**	**79 (90.8)**	**<0.001**
Latino	**14 (11.3)**	**9 (24.3)**	**5 (5.7)**	**<0.001**
Asian	4 (3.2)	2 (5.4)	2 (2.3)	0.262
African	2 (1.6)	1 (2.7)	1 (1.1)	0.163
Female	98 (79)	28 (75.7)	70 (80.5)	0.549
Photosensitivity	63 (50.8)	19 (51.3)	19 (50.6)	0.831
Gottron syndrome	104 (83.9)	30 (81.1)	74 (85.1)	0.622
Heliotrope rash	77 (62.1)	24 (64.9)	53 (60.9)	0.216
Poikiloderma	64 (51.6)	18 (48.6)	46 (52.9)	0.362
Periungual involvement	99 (79.8)	31 (83.8)	68 (78.2)	0.317
Antisynthetase syndrome	7 (5.6)	1 (2.7)	6 (6.9)	0.353
Oral injuries	**12 (9.7)**	**6 (16.2)**	**6 (6.9)**	**0.004**
Alopecia	**37 (29.8)**	**14 (37.8)**	**23 (26.4)**	**0.016**
Diffuse	**30 (24.2)**	**11 (29.7)**	**17 (19.5)**	**0.041**
Cicatricial	7 (5.6)	3 (8.1)	4 (4.6)	0.115
Calcinosis of the skin	11 (8.8)	3 (8.1)	8 (9.2)	0.726
Raynaud	22 (17.7)	7 (18.9)	15 (17.2)	0.682
Mechanic's hands	**12 (9.7)**	**6 (16.2)**	**6 (6.9)**	**0.004**
Panniculitis	9 (7.6)	4 (10.8)	5 (5.7)	0.073
Muscular weakness	**85 (68.5)**	**18 (48.6)**	**67 (77.0)**	**<0.001**
Mild	23 (18.5)	9 (24.3)	14 (16.1)	0.141
Moderate	36 (29.0)	6 (16.2)	30 (24.2)	0.132
Severe	**26 (21.0)**	**3 (8.1)**	**23 (26.4)**	**<0.001**
Arthritis	**28 (22.6)**	**14 (37.8)**	**14 (16.1)**	**<0.001**
Axial	0 (0.0)	0 (0.0)	0 (0.0)	-
Peripheral	**9 (7.6)**	**5 (13.5)**	**4 (4.6)**	**<0.001**
Both	3 (2.4)	1 (2.7)	2 (2.3)	0.742
Acral	**16 (12.9)**	**8 (21.6)**	**8 (9.2)**	**<0.001**
Pulmonary involvement	**28 (22.6)**	**18 (48.6)**	**10 (11.5)**	**<0.001**
Interstitial pneumonitis	**28 (22.6)**	**18 (48.6)**	**10 (11.5)**	**<0.001**
Altered PFT	**17 (13.7)**	**10 (27.0)**	**7 (8.0)**	**0.005**
Ground-glass opacities	**15 (12.1)**	**11 (29.7)**	**4 (4.6)**	**<0.001**
RP-ILD	3 (2.4)	2 (5.4)	1 (1.1)	0.158
Cancer	26 (20.9)	6 (16.2)	20 (16.1)	0.886
Cardiac involvement	7 (5.6)	3 (8.1)	4 (4.6)	0.115

Dysphagia	23 (18.5)	9 (24.3)	14 (16.1)	0.141
Palmar papules	**24 (19.3)**	**17 (45.9)**	**7 (8.0)**	**<0.001**
Dorsal papules	**39 (31.4)**	**17 (45.9)**	**22 (25.3)**	**0.002**
Painful dorsal papules	11 (28.2)	5 (29.4)	6 (27.6)	0.883
Digital tip involvement	**18 (14.5)**	**14 (37.8)**	**4 (4.6)**	**<0.001**
Palmar erythema	**29 (23.4)**	**18 (48.6)**	**11 (12.6)**	**<0.001**
Hyperkeratosis in the proximal nail fold	48 (38.7)	19 (51.4)	29 (33.3)	0.059
Skin ulceration	**62 (50.0)**	**36 (97.3)**	**26 (29.9)**	**<0.001**
Cutaneous	**24 (19.3)**	**14 (37.8)**	**10 (8.1)**	**<0.001**
Acral	**10 (8.0)**	**7 (18.9)**	**3 (3.4)**	**<0.001**
Trunk	4 (3.2)	1 (2.7)	3 (3.4)	0.635
Member root	**7 (5.6)**	**4 (10.8)**	**3 (3.4)**	**0.025**
Oral	8 (6.4)	4 (10.8)	4 (4.6)	0.198
Others	**9 (7.6)**	**6 (16.2)**	**3 (3.4)**	**<0.001**
Biopsy palmar injuries	2 (1.6)	1 (2.7)	1 (1.1)	0.152
Vasculopathy	**7 (5.6)**	**6 (16.2)**	**1 (1.1)**	**<0.001**
Elevated liver enzymes	**47 (37.9)**	**19 (51.3)**	**28 (32.2)**	**0.007**
AST, UI/l [IQR]	88.5 [60.0-128.75]	96.0 [68.5-117.0]	85.5 [63.5-121.0]	0.224
ALT, UI/l [IQR]	107.0 [69.0-191.0]	100.5 [71.5-183.5]	113.0 [67.5-189.5]	0.339
GGT, UI/l [IQR]	121.0 [76.0-289.25]	120.0 [75.5-277.5]	121.5 [77.0-289.0]	0.931
Elevated Ferritin	**24 (19.4)**	**14 (37.8)**	**10 (11.5)**	**0.003**
Elevated LDH	68 (54.3)	20 (54.0)	48 (55.2)	0.917
Elevated CK	**58 (46.8)**	**11 (29.7)**	**47 (54.0)**	**<0.001**
Elevated ESR	**53 (42.7)**	**21 (56.7)**	**32 (36.8)**	**0.007**
Elevated lymphopenia	**36 (29.0)**	**15 (40.5)**	**21 (24.1)**	**<0.001**
Elevated eosinophilia	5 (4.0)	0 (0.0)	5 (5.7)	0.362
ANA	79 (63.7)	21 (56.8)	58 (66.7)	0.294
Anti SSA/Ro	18 (14.5)	5 (13.5)	13 (14.9)	0.836
Anti $Ro52^{+}$	22 (17.7)	10 (27.0)	12 (13.8)	0.078
Anti SSB/La	0 (0.0)	0 (0.0)	0 (0.0)	-
Anti TIF-1 gamma	**21 (16.9)**	**1 (2.7)**	**20 (23.0)**	**0.006**
Anti Jo-1	**9 (7.3)**	**0 (0.0)**	**9 (10.3)**	**0.042**
Anti Mi-2	**11 (8.9)**	**0 (0.0)**	**11 (12.6)**	**0.023**
Anti SAE	5 (4.0)	0 (0.0)	5 (5.7)	0.137
Anti NXP2	2 (1.6)	0 (0.0)	2 (2.3)	0.352
Anti KU	2 (1.6)	1 (2.7)	1 (1.1)	0.53
PL-7	1 (0.8)	1 (2.7)	0 (0.0)	0.124
Decreased C4	7 (5.6)	1 (2.7)	6 (6.9)	0.355
Anti CCP	2 (1.6)	1 (2.7)	1 (1.1)	0.53
RF	8 (6.5)	1 (2.7)	7 (8.0)	0.268

ANA, antinuclear antibodies; anti CCP, anti-cyclic citrullinated peptide; Anti Mi-2, anti-complex nucleosome remodeling histone deacetylase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase; IQR, Interquartile range; Jo-1, Histidyl-tRNA synthetase; LDH, lactate dehydrogenase; NXP2, nuclear matrix protein 2; PFT, pulmonary function testing; PL7, anti-threonine-ARN-t-synthetase; RP-ILD: rapidly progressive interstitial lung disease; RF, rheumatoid factor; SAE, anti-small ubiquitin-like modifier activating enzyme; SD, Standard deviation; TIF-1 gamma, Transcription intermediary factor 1-γ.

Table 3. Multivariate analysis with predictive anti-MDA5^{+} variables.

	OR	95% CI	*P*
Vasculopathy	12.355	2.850-79.263	0.012
Arthritis	9.823	1.559-61.877	0.015
Digital tip involvement	7.447	2.103-46.718	0.004
Elevated ferritin	7.143	1.517-33.654	0.013
Pulmonary involvement	6.384	1.152-35.372	0.034
Muscle weakness	0.076	0.012-0.487	0.006
Anti TIFF-1 gamma	0.007	0.000-0.308	0.011

95% CI, 95% Confidence intervals; OR, Odds Ratio; TIF-1 gamma, Transcription intermediary factor 1-γ