Case report • DOI: 10.2478/pneum-2023-0007 • 70 • 2021 • 46-52

Pneumologia

Clinical and therapeutic features of myositis associated with anti-MDA5 antibodies: three new cases

Donia Chebbi[1,*], Mouna Snoussi[1], Chifa Damak[1], Mouna Guermazi[1], Hend Hachicha[2], Faten Frikha[1], Raida Ben Salah[1], Hatem Masmoudi[2], Sameh Marzouk[1], Zouhir Bahloul[1]

[1]Department of Internal Medicine, Hedi Chaker University Hospital, Sfax, Tunisia
[2]Department of Immunology, Hedi Chaker University Hospital, Sfax, Tunisia

Abstract

English:

Purpose: *To assess clinical features, therapy, and outcome of the myositis associated with anti-MDA5 antibodies, and to propose a successful therapeutic protocol for rapidly progressive interstitial lung disease (RP-ILD) in anti-MDA5 dermatomyositis (DM).*
Methods: *A retrospective and descriptive study of three cases of anti-MDA5 associated myositis was conducted in the Department of Internal Medicine in the University Hospital Hedi Chaker, Sfax, Tunisia, between 1996 and 2016.*
Results: *From a series of 115 cases of myositis, three cases of anti-MDA5-positive DM were identified. They were three men with a mean age of 63 years. They manifested specific cutaneous manifestations including ulcers and palmar papules, mild muscular involvement, and RP-ILD. The severity of the disease was correlated to the ILD in all patients. Aggressive therapies were tried including high-dose corticoids, cyclophosphamide (CYC) cures, intravenous immunoglobulins, and rituximab (RTX), with a good outcome in the patient who received combined high steroids, CYC, and RTX pulses. The two other patients died because of a rapid worsening of their respiratory condition.*
Conclusion: *Anti-MDA positive myositis is characterised by a specific cutaneous phenotype, the discretion of muscular signs, and the correlation with RP-ILD. The poor prognosis of this entity is correlated to the high resistance of pulmonary involvement despite aggressive therapeutics. The combination between high-dose steroids, CYC, and RTX has shown good results in many reports, as well as in one of our patients.*

Keywords

dermatomyositis • anti-MDA5 antibody • interstitial lung disease • cryptogenic organising pneumonia • rituximab

Caracteristici clinice si terapeutice in miozita asociata cu anticorpi anti-MDA5: trei cazuri clinice noi

Rezumat

Romanian:

Obiectiv: *Evaluarea caracteristicilor clinice, terapeutice si evolutive in miozita asociata cu anticorpi anti-MDA5 si propunerea unui protocol terapeutic eficient in cazul pneumopatiei interstitiale cu progresie rapida (RP-ILD) asociata dermatomiozitei (DM) cu anticorpi anti-MDA5.*
Metode: *Au fost studiate retrospectiv si descriptiv trei cazuri de miozita cu anticorpi anti-MDA5 internate in Departamentul de Medicina Interna al Spitalului Universitar Hedi Chaker, Sfax, Tunisia, intre 1996 si 2016.*
Rezultate: *Au fost identificate trei cazuri de miozita anti-MDA5 pozitive dintr-o serie de 115 cazuri de miozita. Toti erau barbati cu o medie de varsta de 63 ani. Manifestarile clinice au fost leziuni cutanate specifice – ulceratii si papule palmare, afectare musculara usoara si RP-ILD. Severitatea bolii a fost corelata cu ILD in toate cazurile. Tratamentul imunosupresor a fost agresiv si a constat in doze inalte de corticosteroizi, cure de ciclofosfamida (CYC), imunoglobuline intravenoase si Rituximab (RTX), cu un rezultat favorabil in cazul unuia dintre pacienti care a primit o combinatie de corticosteroizi in doza mare, CYC si pulsuri de RTX. Ceilalti doi pacienti au decedat ca urmare a inrautatirii rapide a conditiei respiratorii.*
Concluzii: *Miozita pozitiva anti-MDA este caracterizata printr-un fenotip cutanat specific, discretia manifestarilor musculare si corelarea cu RP-ILD. Prognosticul infaust al acestei entitati este dat de rezistenta la tratamentele agresive imunosupresoare a afectarii interstitiale pulmonare. Combinatia dintre steroizi in doza inalta, CYC si RTX a adus rezultate favorabile atat in cazul unuia dintre pacientii nostri, cat si in alte rapoarte din literatura.*

Cuvinte-cheie

Dermatomiozita • anticorpi anti-MDA5 • boala pulmonara interstitiala • pneumonie criptogenica in organizare • Rituximab

*Corresponding author: Donia Chebbi
E-mail: doniachebba@gmail.com

Open Access. © 2021 Chebbi et al., published by Sciendo
This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License.

Introduction

Dermatomyositis (DM) is an inflammatory autoimmune disease affecting skin, muscles, and lungs in different ways and to variable degrees. The existence of specific autoantibodies allows a better characterisation of the disease: clinical phenotypes, prognosis, and response to the available therapies (1). The autoantibody targeting melanoma differentiation-associated protein 5 (MDA5) is a new specific antibody, described for the first time by Sato in 2003 (2). It is typically associated with a clinically amyopathic DM (CADM), specific cutaneous manifestations including ulcerations and necrosis, and fatal rapidly progressive interstitial lung disease (RP-ILD) (3).

Objectives

We report three new cases of myositis associated with anti-MDA5 antibodies to assess the clinical features, therapy, and outcome of this entity. We also propose a successful therapeutic protocol for RP-ILD in anti-MDA5 DM.

Patients and methods

We collected the data of patients presenting with myositis between 1998 and 2018, in the department of Internal Medicine of Hedi Chaker University Hospital in Sfax, Tunisia. We retrospectively reviewed the disease onset, the demographic findings (including age and sex), the clinical symptoms, the laboratory data, and the imaging findings. The laboratory data included routine biochemical and haematological tests, ferritin, blood gas analysis, antinuclear antibodies (ANA), and myositis-associated autoantibodies including antihistidyl-tRNA synthetase (Jo-1), anti-aminoacyl transfer RNA synthetase (ARS), and anti-MDA5. The diagnosis of myositis was established using the Bohan and Peter (4) criteria. We also evaluated therapy and major clinical outcomes including survival, comorbidities, and complications.

Results

Three patients with clinical and serological anti-MDA5-positive DM were identified among a series of 115 cases (2%) of DM and PM.

All patients were males, with a mean age of 63 years (52, 57, and 80 years). The disease onset was subacute in all cases (1 month), and the revealing symptoms were asthenia and fever in one patient and respiratory signs in two patients.

Physical examination upon admission revealed erythroedema in all the patients (Figure 1), cutaneous ulcers in two cases (Figures 1 and 2), skin and mucous membrane ulcers in one case, periungual erythema in one case, ulcerated palmar papules in one case (Figure 3), and scaly hypopigmented erythematous lesions of the scalp in one case (Figure 4).



Figure 1. Periorbital erythema + facial ulceration (red arrow).



Figure 2. Erythematous ulcerous lesion of the elbow.

Skin biopsy made in one case was consistent with DM findings, revealing an interface dermatitis with epidermal basal cell vacuolar degeneration and a lymphocytic inflammatory infiltrate of the superficial dermis.

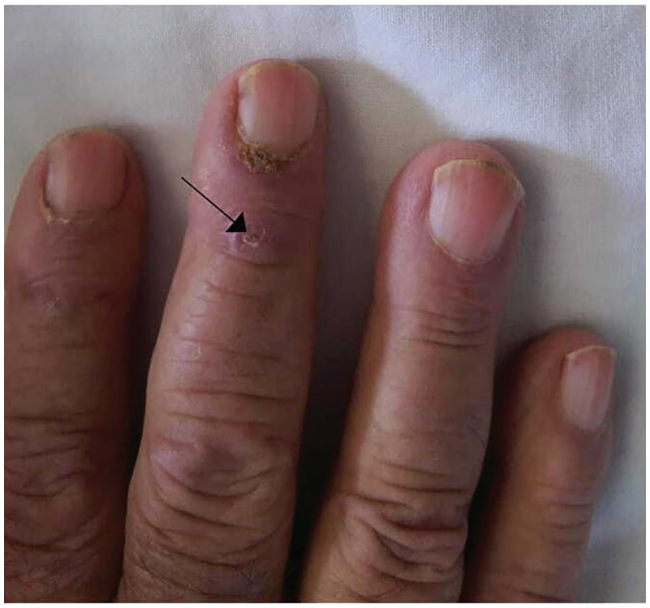


Figure 3. Erythematous and ulcerated palmar papules (black arrow).



Figure 4. Scaly hypopigmented scalp lesions.

The muscular involvement was attenuated in all the patients, and muscular testing showed a moderate proximal extremities weakness (3/5) in two patients and no weakness in the third one. Only one patient presented mild dysphagia. Although the serum creatine phosphokinase (CPK) level was lower than twice the upper limit in the three patients, the electromyogram showed a typical myogenic pattern in the four limbs in two patients. It was normal in the third case. Histopathology of a muscle biopsy was performed on only one of our patients, disclosing a polymyositis aspect (necrosis and regeneration lesions with peri-fascicular atrophy and micro-infarction).

The severity of the disease was related to serious rapidly progressive pulmonary involvement in all the patients. Clinically, they presented a cough and progressive worsening dyspnoea. The chest CT scan showed nonspecific interstitial pneumonia (NSIP) in two cases, and diffuse interstitial lung disease (ILD) with cryptogenic organising pneumonia (COP) in one case (Figure 5). Besides, pulmonary function tests (PFT) performed on one patient revealed mild restrictive and severe obstructive syndrome. The latter also presented bilateral paralysis in the diaphragmatic EMG.

Articular involvement concerned only one patient who had symmetric synovitis of the proximal interphalangeal joints and the wrists, with negative rheumatoid and anti-cyclic citrullinated peptide (anti-CCP) serologies. Apart from myolysis, laboratory tests also showed hyperferritinemia reaching 1175 ng/mL in one case. High erythrocyte sedimentation rate (ESR) and high C-reactive protein (CRP) levels were also noted in all patients.

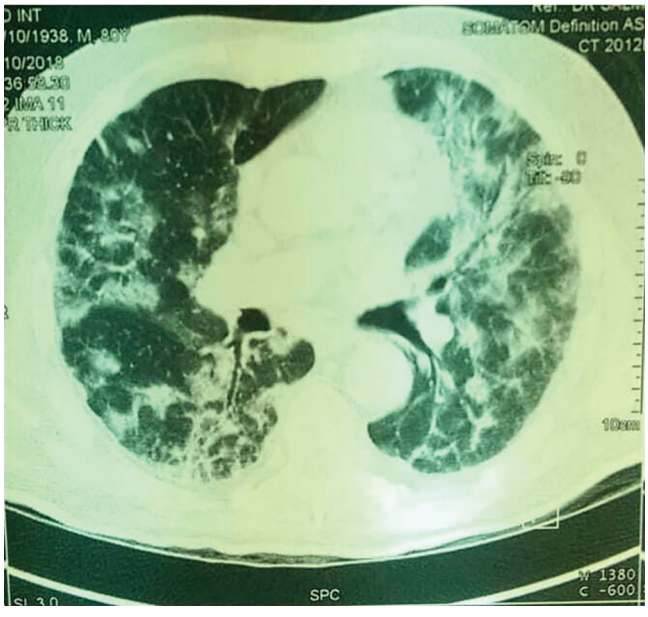


Figure 5. Chest CT scan imaging; cross-section showing COP. COP, cryptogenic organising pneumonia; CT, computed tomography.

Tests for extractable nuclear antigens (ENA) identified positive anti-Ro52 antibodies in all cases, as well as tests of myositis-specific antibodies that identified positive anti-MDA5 antibodies in 100% of the cases. Thus, our patients were diagnosed with anti-MDA5 DM. The important loss of body weight in addition to lower urinary tract symptoms raised the suspicion of a paraneoplastic DM in one patient. Indeed, the prostate-specific antigen (PSA) level was >60 ng/mL, and the biopsy revealed prostate adenocarcinoma. However, there was no evidence of malignancy in the two other cases.

Treatment with intravenous methylprednisolone pulses was indicated in all the cases, followed by a high dose of corticosteroid therapy (1 mg/kg/day prednisolone). Yet, all the patients underwent rapid deterioration in their respiratory conditions. The first one died rapidly in 1 week. In the second case, we opted for cyclophosphamide (CYC) as a second-line therapy, without any improvement. The patient's dyspnoea worsened and he presented severe hypoxia. After the second CYC pulse, we added rituximab (RTX) using the protocol of two 1000-mg intravenous infusions separated by 2 weeks. Good results were observed since the first cure. In fact, we noted a gradual improvement of the dyspnoea, and a regression of the dysphagia, muscular weakness, and cutaneous manifestations. Serum ferritin concentrations normalised, as well as ESR and CRP. This patient received a total of 12 monthly CYC pulses followed by four quarterly ones. He then had a maintenance bolus of RTX. The thoracic CT scan performed at 1 year of follow-up showed an important regression of the interstitial lung lesions. Besides, functional parameters normalised in the PFT. At a 3-year follow-up, the patient is still in remission without immunosuppressive (IS) treatment.

The third patient experienced worsening of his dyspnoea despite the use of CYC and veinoglobulin cures.

Demographic data, clinical findings, laboratory test results, medical therapy, and outcome of all three patients are presented in Table 1.

Discussion

In the present study, we reported three cases of anti-MDA5 DM among a series of 115 cases of DM (2%) followed in the Department of Internal Medicine, Hedi Chaker University Hospital, Sfax, Tunisia.

The positivity for anti-MDA5 autoantibody can vary from 4.7% to 14.7% in DM according to the literature. It is more important in the group of clinically amyopathic DM, reaching 18.8% (5).

Mucocutaneous features of anti-MDA5 DM

The anti-MDA5 would constitute an immunological marker of a specific dermatological phenotype of adult DM. Ulcers

Table 1. Main clinical and demographic characteristics in our patients.

	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Age at onset (years)	80	52	57
Smoking history	-	+	-
Medical background	Type 2 diabetes, coronary insufficiency	Type 2 diabetes, high blood pressure	None
Malignancy	Adenocarcinoma of the prostate	-	-
Cutaneous features	Periorbital erythroderma Ulcers (elbows, knees, face)	Periorbital erythroderma Ulcers (elbows, back, chest) Periungual erythema Ulcerated palmar papules Scaly erythematous Hypopigmented lesions of the scalp	Periorbital erythroderma Gottron papules (elbows)
MSK	Hypomyopathic CPK 1.5*normal	Polyarthritis Hypomyopathic CPK 2*normal Dysphagia	Hypomyopathic CPK 1.5*normal
ILD onset	Immediately	During follow-up	Immediately
Positive serologies	MDA5+ ANA+ (1/320) Ro52+	MDA5+ ANA+ (1/1280) SSA+ Ro52+	MDA5+ ANA+ (1/640)
Medical therapy	MP, OS	MP, OS, CYC, RTX	MP, OS, CYC, IVIG
Follow-up	1 week	3 years	2 weeks
Outcome	Died (respiratory distress)	Remission	Died (respiratory distress)

ANA, antinuclear antibodies; CPK, creatine phosphokinase; CYC, cyclophosphamide; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; MDA5, melanoma differentiation-associated protein 5; MP, methylprednisolone pulse; MSK, musculoskeletal; OS, oral steroids; RTX, rituximab; SSA, anti-sicca syndrome A.

are one of the most characteristic signs, found in 82% of the cases, usually deep and covered with crusts. They may involve digital pulps or cover Gottron papules in the hands, the elbows, or the knees. Photo-exposed areas such as the chest, back, and arm are less commonly involved. These ulcerations are often a cause of severe pain, necrosis, and significant morbidity (6,7).

Palmar papules are also significantly associated with anti-MDA5 autoantibodies. They are often keratotic, ivory-coloured, painful, ulcerated, and located on the palmar creases of the fingers and palms (6,8).

Diffuse alopecia, mechanical hands, Gottron sign on the extension surfaces of the elbow and the knee, and ulceration of the oral mucosa are other signs significantly associated with the positivity of anti-MDA5-autoantibodies.

Two of our patients presented specific mucocutaneous manifestations consisting of ulcerations in the face, the elbows, and the knees, and these were more diffuse in the second case, involving the back, the arms, and the oral mucosa. Ulcerated palmar papules were observed in one case.

Pulmonary manifestations of anti-MDA5 DM

Interstitial lung disease (ILD) is the most specific pulmonary manifestation. It has been even proven that the positivity of anti-MDA5 antibodies predicts a high risk of developing ILD in polymyositis/DM patients with high sensitivity (77%) and high specificity (86%), regardless of ethnic origin (9). On the other hand, the prevalence of ILD in anti-MDA5 DM has been estimated between 92% and 100% in Asian cohorts (7,10–12) and between 50% and 73% in European and US studies (6,7,13–15).

ILD is severe, hypoxemic, rapidly progressive, and therapy-resistant in most of these reports (15–17). The high-resolution computed tomography (HRCT) of the chest is the most sensitive imaging technique in the detection of ILD. The most frequent radiological patterns are NSIP and organized pneumonia. Some scannographic particularities have been reported: the predominance of ground glass opacities and the absence of intralobular reticulations (7,18,19).

In agreement with previous reports, all our patients manifested severe rapidly progressive hypoxemic respiratory failure due to myositis-related ILD. Scannographic aspects in our patients were NSIP and ILD with COP.

Pneumomediastinum is another pulmonary manifestation, significantly related to the positivity of anti-MDA5-autoantibodies (20).

Other systemic features of anti-MDA5 DM

The clinical phenotype of patients with these autoantibodies is characterised by the discretion or the absence of muscular involvement (19). All of our patients manifested moderate muscular weakness with a slight rise in CPK that was no more than twice the upper limit.

Symmetric polyarthritis, observed in our second patient, is often reported. Rheumatoid factor and CCP are typically negative in these cases (13).

Anti-MDA5 DM and malignancy

While the association of DM and neoplasia have been well demonstrated (21), the positive MDA5-antibodies DM appears to be less correlated to cancers than classic DM (22,23). This rare association was noted in one of our patients who was diagnosed with prostate cancer.

Treatment options and prognosis

Treatment of ILD associated with anti-MDA5 DM is based on corticosteroids and IS agents, as in classic DM. However, ILD is often RP-ILD, therapy-resistant, and fatal (3,24,25).

Recommendations for treatment strategies for RP-ILD associated with anti-MDA5 do not exist yet. McPherson et al. (26) collected in their systematic review all the trials, cohort studies, and case series assessing treatment options for this condition. Only one randomised controlled trial is reported in the literature. The initial use of combined IS drugs was an overall agreement. The combination of high-dose systemic glucocorticoids and IS agents such as CYC and/or calcineurin inhibitors (cyclosporine or tacrolimus) is initially indicated. If the disease is refractory, other therapeutic options are added, such as plasma exchange, RTX, or tofacitinib (27).

Focussing on RTX use, a Chinese trial, conducted in Hong Kong between 2015 and 2017, studied the effect of RTX on four patients diagnosed with RP-ILD in the context of anti-MDA5 DM. The disease did not respond to high-dose systemic steroid and other intensive IS therapies. Satisfactory results were observed with RTX: improvement in the respiratory symptoms and the lung function tests in all the cases, and reduction in HRCT lesions in three patients, while the other one remained static. No deaths were reported throughout the follow-up period ranging from 6 months to 2 years. However, two patients developed a chest infection. These results suggest that RTX may be an interesting treatment modality for anti-MDA5 DM associated with ILD, with major infection risk (28).

Early diagnosis and early treatment are the first steps of good management, especially in the case of ILD. Indeed, ILD should be screened even in asymptomatic patients, using PFT and DLCO, and HRCT if any abnormality is detected (7).

The prognosis of anti-MDA5 DM with ILD is poor, especially in RP-ILD. This complication is life-threatening even under aggressive IS therapies (11,25). In fact, the 6-month survival rate in two cohorts of clinically amyotrophic DM patients with RP-ILD was estimated as 40.8%–45.0% (9,25).

Mortality occurs most often during the first 6 months of the disease. In fact, it seems that ILD stops getting worse if the patient survives beyond 6 months (19,29). Factors associated with poor prognosis and death include hyperferritinemia ≥830 mg/mL and a high anti-MDA5 autoantibody index (29,30). Age does also influence mortality according to a new Japanese study, proving that patients aged ≥60 years had a worse prognosis (22). Anti-Ro52 may also be a prognosis factor, contributing to a more severe ILD. However, these results were not statistically significant (31,32).

In our series, mortality reached two-third of the cases, despite the combination of high-dose corticosteroids, CYC, and immunoglobulin in one patient. In the other case, high-dose steroid therapy was insufficient to prevent rapid death in 1 week.

The poor prognosis factors in our series were RP-ILD in all the cases, age >60 years in one case, hyperferritinemia in one case, and anti-Ro52 in two cases.

The surviving patient was the youngest (52 years). We propose through this case a successful treatment regimen for anti-MDA5-DM RP-ILD based on the association of high-dose steroid therapy, 12 monthly cures followed by four quarterly cures of CYC, and three cures of RTX (two for induction and one as maintenance therapy).

Our work has some limitations, especially the small number of cases. Nevertheless, we could highlight through these cases many particularities of the positive anti-MDA5 DM, including the specific cutaneous phenotype, the discretion of muscular signs, the correlation with RP-ILD, the poor prognosis and the high resistance of this pulmonary involvement to aggressive therapies, and the efficiency of the combination of high-dose steroids, CYC, and RTX.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no potential conflict of interest relevant to this article.

References

1. Gunawardena H, Betteridge ZE, McHugh NE. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. *Rheumatology*. 2009;48(6): 607–612.
2. Sato, S. Clinical and immunological associations of autoantibodies to the 140kDa polypeptide (the US autoantigen) in patients with clinically amyopathic dermatomyositis. *Arthritis and Rheumatology*. 2003;48(9): 102.
3. Damoiseaux J, Vulsteke J, Tseng C, Platteel ACM, Piette Y, Shovman O, et al. Autoantibodies in idiopathic inflammatory myopathies : clinical associations and laboratory evaluation by mono- and multispecific immunoassays. *Autoimmunity Reviews*. 2019;18(3): 293–305. doi:10.1016/j.autrev.2018.10.004.
4. Bohan A, Peter JB. Polymyositis and dermatomyositis. *The New England Journal of Medicine*. 1975;292: 344–347.
5. Borges IBP, Silva MG, Shinjo SK. Prevalence and reactivity of anti-melanoma differentiation-associated gene 5 (anti-MDA-5) autoantibody in Brazilian patients with dermatomyositis*. *Anais Brasileiros de Dermatologia*. 2018;93(4): 517–523.
6. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. *Journal of the American Academy of Dermatology*. 2011;65(1): 25–34. doi:10.1016/j.jaad.2010.09.016.
7. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *Journal of the American Academy of Dermatology*. 2018;78(4): 776–785. doi:10.1016/j.jaad.2017.12.010.
8. Girard C, Vincent T, Bessis D. Dermatomyosite et pneumopathie interstitielle rapidement évolutive associées aux auto-anticorps anti-MDA-5 : une présentation clinique atypique. *Annales de Dermatologie et de Vénéréologie*. 2013;140(10): 628–634. doi:10.1016/j.annder.2013.04.083.
9. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care and Research (Hoboken)*. 2013;65(8): 1316–1324.
10. Koga T, Fujikawa K, Horai Y, Okada A, Kawashiri SY, Iwamoto N, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. *Rheumatology (Oxford)*. 2012;51(7): 1278–1284.
11. Cao H, Pan M, Kang Y, Xia Q, Li X, Zhao X, et al. Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. *Arthritis Care and Research (Hoboken)*. 2012;64(10): 1602–1610.
12. Nakashima R, Imura Y, Kobayashi S, Yukawa N, Yoshifuji H, Nojima T, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. *Rheumatology (Oxford)*. 2010;49(3): 433–440.

13. Hall JC, Casciola-Rosen L, Samedy LA, Werner J, Owoyemi K, Danoff SK, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. *Arthritis Care and Research (Hoboken)*. 2013;65(8): 1307–1315.
14. Ceribelli A, Fredi M, Taraborelli M, Cavazzana I, Tincani A, Selmi C, et al. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. *Clinical and Experimental Rheumatology*. 2014;32(6): 891–897.
15. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Anti-melanoma differentiation-associated gene 5 is associated with rapidly progressive lung disease and poor survival in US patients with amyopathic and myopathic dermatomyositis. *Arthritis Care and Research (Hoboken)*. 2016;68(5): 689–694.
16. Gil B, Merav L, Pnina L, Chagai G. Diagnosis and treatment of clinically amyopathic dermatomyositis (CADM): a case series and literature review. *Clinical Rheumatology*. 2016;35: 2125–2130.
17. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis and Rheumatism*. 2009;60: 2193–2200.
18. Tanizawa K, Handa T, Nakashima R, Kubo T, Hosono Y, Watanabe K, et al. HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody. *Respiratory Medicine*. 2011;105(9): 1380–1387. doi:10.1016/j.rmed.2011.05.006.
19. Gerfaud-valentin M, Ahmad K, Piegay F, Fabien N, Raphanel B, Cordier JF, et al. Pneumopathie infiltrante diffuse associée à une dermatomyosite amyopathique avec auto-anticorps anti-MDA5. *Revue des Maladies Respiratoires*. 2014;31(9): 849–853. doi:10.1016/j.rmr.2014.02.010.
20. Ma X, Chen Z, Hu W, Guo Z, Wang Y, Kuwana M, et al. Clinical and serological features of patients with dermatomyositis complicated by spontaneous pneumomediastinum. *Clinical Rheumatology*. 2016;35(2): 489–493.
21. Waldman R, DeWane ME, Lu J. Dermatomyositis part 2: diagnosis and treatment. *Journal of the American Academy of Dermatology*. 2019;82(2): 283–296.
22. Yamaguchi K, Yamaguchi A, Onuki Y, Itai M, Kashiwagi C, Takehara K, et al. Clinical features of dermatomyositis associated with anti-MDA-5 antibodies by age. *Modern Rheumatology*. 2020;31(1): 177–185. doi:10.1080/14397595.2020.1740400.
23. Sontheimer RD. MDA5 autoantibody — another indicator of clinical diversity in dermatomyositis. *Annals of Translational Medicine*. 2017;5(7): 160.
24. Yashiro M, Asano T, Sato S, Kobayashi H, Watanabe H, Miyata M, et al. Anti- MDA5 antibody- positive hypomyopathic dermatomyositis complicated with pneumomediastinum. *Fukushima Journal of Medical Science*. 2018;64(2): 89–94.
25. Mukae H, Ishimoto H, Sakamoto N, Hara S, Kakugawa T, Nakayama S, et al. Clinical differences between interstitial lung disease associated with clinically amyopathic dermatomyositis and classic dermatomyositis. *Chest*. 2009;136: 1341–1347.
26. McPherson M, Economidou S, Liampas A, Zis P, Parperis K. Management of MDA-5 antibody positive clinically amyopathic dermatomyositis associated interstitial lung disease: a systematic review. *Seminars in Arthritis and Rheumatism*. 2022;53: 151959.
27. Romero-Bueno F, Diaz Del Campo P, Trallero-Araguás E, Ruiz-Rodríguez JC, Castellvi I, Rodriguez-Nieto MJ, et al. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. *Seminars in Arthritis and Rheumatism*. 2020;50(4): 776–790.
28. So H, Wong VTL, Lao VWN, Pang HT, Yip RML. Rituximab for refractory rapidly progressive interstitial lung disease related to anti-MDA5 antibody-positive amyopathic dermatomyositis. *Clinical Rheumatology*. 2018;37(7): 1983–1989.
29. Gono T, Sato S, Kawaguchi Y, Kuwana M, Hanaoka M, Katsumata Y, et al. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. *Rheumatology (Oxford)*. 2012;51(9): 1563–1570.
30. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, Takagi K, et al. Clinical manifestation and prognostic factor in anti-melanoma differentiation- associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. *Rheumatology Oxford)*. 2010;49(9): 1713–1719.
31. Huang K, Vinik O, Shojania K, Yeung J, Shupak R, Nimmo M, et al. Clinical spectrum and therapeutics in Canadian patients with anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis: a case-based review. *Rheumatology International*. 2019;39(11): 1971–1981. doi:10.1007/s00296-019-04398-2.
32. Labrador-Horrillo M, Martinez MA, Selva-O'Callaghan A, Trallero-Araguas E, Balada E, Vilardell-Tarres M, et al. Anti-MDA5 antibodies in a large Mediterranean population of adults with dermatomyositis. *Journal of Immunology Research*. 2014;2014: 290797.