Cardiac involvement in patients with anti-melanoma differentiation-associated gene-5 antibody-positive dermatomyositis

Y. Wang[1], X. Chen[2], Z. Huang[1], Y. Wang[3], W. Jiang[4], J. Lei[5], S. Xie[1], L. Zhang[4]

[1]Department of Radiology, China-Japan Friendship Hospital, Beijing; [2]Department of Renal and Rheumatology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai; [3]Department of Dermatology, China-Japan Friendship Hospital, Beijing; [4]Department of Rheumatology, Key Myositis Laboratories, China-Japan Friendship Hospital, Beijing; [5]Department of Clinical Research and Data Management, China-Japan Friendship Hospital, Beijing, China.

Abstract

Objective

To investigate cardiac involvement in patients with anti-melanoma differentiation-associated gene-5 antibody-positive dermatomyositis (MDA5-DM).

Methods

This prospective study included 37 patients with MDA5-DM and 31 age- and sex-matched healthy controls (HCs). Electrocardiography, echocardiography (ECHO), and cardiac magnetic resonance (CMR) was performed to assess cardiac involvement. Clinical features were compared between patients with and without CMR abnormalities. Logistic regression analysis was used to explore independent risk factors for CMR abnormalities. Six patients with abnormal CMR findings were followed up.

Results

Three patients complained of chest pain, and nine reported palpitations. The incidence of sinus tachycardia and ST-T changes were 13.5%. Premature atrial/ventricular contractions were detected in three patients. Four patients had decreased left ventricular systolic function on ECHO. 24 patients had abnormal CMR mapping results. Patients had significantly higher values in native T1 ($p<0.001$) and T2 ($p=0.007$) mapping, compared with HCs. Elevated extracellular volume was detected in 45.9% of the patients. Subgroup analysis showed significantly higher constitutional Visual Analogue Scale (VAS) score, cutaneous VAS score, serum NT-proBNP level, and anti-MDA5 antibody titre in patients with abnormal CMR parameters than in those with normal CMR parameters (all $p\leq0.001$). Logistic regression analysis revealed cutaneous VAS score as a risk factor for abnormal CMR ($p=0.033$). Follow-up of six patients with abnormal CMR findings showed significantly improved CMR mapping parameters post-treatment.

Conclusion

Subclinical cardiac involvement was predominant in patients with MDA5-DM and can be sensitively detected by CMR. Cardiac involvement is closely correlated with cutaneous lesions and may improve after treatment with prednisone and immunosuppressants.

Key words

dermatomyositis, anti-melanoma differentiation-associated protein 5 antibody, cardiac involvement, cardiac magnetic resonance

Yuli Wang, MD
Xixia Chen, MD
Zhenguo Huang, MD
Ying Wang, MD
Wei Jiang, MD
Jieping Lei, PhD
Sheng Xie, MD
Lu Zhang, MD, PhD

Please address correspondence to:
Lu Zhang
Department of Rheumatology,
China-Japan Friendship Hospital,
2 Yinghua Road, Chaoyang District,
100029 Beijing, China.
E-mail: zhanglu_1224@sina.com

Received on February 8, 2025; accepted in revised form on May 5, 2025.

Funding: this work was supported by National High Level Hospital Clinical Research Funding (2022-NHLHCRF-YS-02).

Competing interests: none declared.

Introduction

Idiopathic inflammatory myopathies (IIM) are heterogeneous autoimmune disorders that are recognised as complex multisystem diseases with a wide spectrum of organ manifestations. Myo-sitis-specific antibodies (MSAs) play a key role in defining the clinical and pathophysiological subsets of myositis (1). Anti-melanoma differentiation-associated gene-5 positive dermatomyositis (MDA5-DM) is a distinct subtype of IIM characterised by the hallmark rash of dermatomyositis, absent or minimal muscle involvement, and significant interstitial lung disease (ILD) (2). Reports on MDA5-DM-associated myocardial involvement are scarce. In a review, Quintero González *et al*. (3) analysed myocardial involvement in 9 patients with anti-MDA5-DM.

Although myocardial involvement was subclinical in some patients, rapid progression of cardiac lesions could lead to life-threatening consequences (4, 5). Thus, early identification of myocardial involvement can play a crucial role in improving prognosis.

Cardiac magnetic resonance (CMR) imaging has gained prominence in clinical practice because of its high sensitivity and specificity compared to conventional detection methods such as electrocardiography (ECG), echocardiography (ECHO), and the measurement of serological indicators, including high-sensitivity troponin I (hsTnI), and N-terminal pro-brain natriuretic peptide (NT-proBNP) (6). Recent advances in parametric mapping have improved the diagnostic accuracy of non-ischaemic myocardial inflammation, resulting in the inclusion of CMR mapping parameters in the updated Lake Louise criteria (7). Thus, measuring CMR mapping parameters has become a critical component of clinicians' diagnostic approaches, facilitating a comprehensive and accurate evaluation of non-ischaemic myocardial inflammation.

This study aimed to investigate cardiac involvement in patients with MDA5-DM using conventional detection methods and CMR and to analyse the risk factors for cardiac involvement.

Methods

Study population

A total of 37 patients with MDA5-DM were prospectively enrolled between January 2023 and October 2024. IIM was diagnosed according to the Bohan and Peter criteria (8) and confirmed based on the 2017 European League against Rheumatism/American College of Rheumatology IIM classification criteria (9). The inclusion criteria were as follows: 1) age ≥18 years and <65 years; 2) willingness to participate in the study and undergo CMR examination; 3) no history of metal implants, claustrophobia, or other MRI contraindications. The exclusion criteria were as follows: 1) malignancy or overlap syndromes; 2) congenital heart disease, rheumatic heart disease, hypertension, coronary artery disease, cardiomyopathy; 3) diabetes, dysthyroidism, severe renal disease (creatinine ≥133 μmol/L), or anaemia; (4) active infections. The control group consisted of 31 healthy controls (HCs) matched for age and sex with no history of cardiovascular or systemic disease who underwent CMR without gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA; Magnevist, Bayer, Berlin, Germany) injections during the same period.

The study protocol was approved by the Ethics Committee (ref. no.: 2022-KY-156), and written informed consent was obtained from all participants.

Clinical data

Patient-related demographic information, clinical characteristics, laboratory test results, chest high resolution computed tomography (HRCT), and pulmonary function tests (PFTs) were recorded within 1 week at enrolment and the follow-up data was collected among patients who received at least 6 months of treatment.

Auxiliary examinations included serum creatine kinase (reference range: 26–200 U/L), hsTnI (reference range: <0.0116 ng/mL), NT-proBNP (reference range: <125 pg/mL), ECG, and ECHO. The criteria used to define infection were based on definitive etiological evidence from laboratory test results, according to previous literature (10). The presence of ILD was assessed

using chest HRCT, and rapidly progressive interstitial lung disease (RP-ILD) was defined using previously established criteria (11). According to the classification criteria of the American Thoracic Society/European Respiratory Society (ATS/ERS) for idiopathic interstitial pneumonias (12), MDA5-DM-ILD can be categorised into the following subtypes: non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), NSIP+OP, diffuse alveolar damage and usual interstitial pneumonia.

Disease activity was assessed at the first and subsequent follow-up visits using core measures developed by the International Myositis Assessment and Clinical Studies Group (13). Muscle strength was assessed using the 8-item Manual Muscle Testing (14). Using the Myositis Disease Activity Assessment Tool, we assessed the disease activity of the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and muscle organ systems using a Visual Analogue Scale (VAS; range: 0–10).

Autoantibody detection

MSAs and myositis-associated antibodies, including anti-MDA5 and anti-Ro-52 antibodies, were identified using immunoblotting according to the manufacturer's instructions (Euroimmun, Lübeck, Germany). An enzyme-linked immunosorbent assay kit (MBL, Tokyo, Japan) was used to determine the anti-MDA5 antibody (anti-MDA5ab) titre, with a cut-off value of 32 U/mL.

CMR protocol

The first CMR data was collected within 1 week at enrolment and the follow-up CMR scans were performed among patients who received at least 6 months of treatment. CMR images were acquired using a 1.5-T scanner (MAGNETOM Area; Siemens Healthcare, Erlangen, Germany) with an 18-channel phase array coil combined with a spine coil. Cine images were obtained using an ECG-gated two-dimensional balanced steady-state free precession sequence. Left ventricular (LV) functional metrics, including end-diastolic volume index (EDVI), end-systolic volume index (ESVI), LV ejection fraction (LVEF), cardiac index and LV mass index (LVMI), was analysed using the cine sequence on Cardiac Function (Syngo-Via workstation Siemens Healthcare, Erlangen, Germany).

T2-weighted short tau inversion recovery images were acquired on short-axis planes covering the entire left ventricle. Late gadolinium enhancement (LGE) images were collected 8–15 min after

Table I. Characteristics of the patients with MDA5-DM.

Variables	Overall (n=37)
General characteristics	
Age at initial visit, mean ± SD, years	41.6 ± 11.2
Male, n (%)	21 (56.8)
Disease duration, median (IQR), months	7 (2, 20)
ILD, n (%)	35 (94.6)
Nonspecific interstitial pneumonia (NSIP), n (%)	16 (43.2)
Organising pneumonia (OP), n (%)	14 (37.8)
NSIP+OP, n (%)	4 (10.8)
Usual interstitial pneumonia, n (%)	1 (2.7)
Diffuse alveolar damage, n (%)	0 (0)
RPILD, n (%)	14 (37.8)
Clinical features at initial visit	
Heliotrope rash, n (%)	22 (59.5)
Gottron's sign, n (%)	33 (89.2)
Mechanic's hand, n (%)	10 (27)
Distal digital tip ulceration, n (%)	12 (32.4)
V sign, n (%)	26 (70.3)
Shawl sign, n (%)	14 (37.8)
Myalgia, n (%)	21 (56.8)
Chest pain, n (%)	3 (8.1)
Palpitation, n (%)	9 (24.3)
Dysphagia, n (%)	6 (16.2)
Prior viral infection, n (%)	12 (32.4)
Prior bacterial infection, n (%)	5 (13.5)
Prior fungal infection, n (%)	5 (13.5)
MMT8 (0-80), median (IQR)	78 (71, 80)
Laboratory findings	
Creatine kinase (ref 26-200), median (IQR), U/L	45 (29, 94)
NT-proBNP (ref<125), median (IQR), pg/mL	76 (37, 228)
hsTnI (ref<0.0116), median (IQR), ng/ml	0.0031 (0.0020, 0.0052)
Anti-Ro-52 antibody positive, n (%)	16 (43.2)
Anti-MDA5ab titre (ref<32), mean ± SD, U/mL	117.87 ± 55.11
ECG	
Heart rate, mean ± SD, beats/min	93 ± 14
Sinus tachycardia, n (%)	5 (13.5)
Premature atrial/ventricular contraction, n (%)	3 (8.1)
ST-T changes	5 (13.5)
ECHO	
LVEDD (ref<55(M), ref<50(F)), median (IQR), mm	46.5 (43.0, 49.0)
LVESD (ref <35), median (IQR), mm	30.0 (26.0, 32.3)
IVST (ref<11), median (IQR), mm	9.8 (8.0, 10.0)
LVEF (ref 50-70), median (IQR), %	66.0 (64.0, 70.0)
E/A (ref>1), mean ± SD	1.57 ± 0.15
Treatment	
Prednisone dose, mg/day	28.99 ± 15.72
Immunosuppressants	
Cyclosporine, n (%)	21 (56.8)
Tacrolimus, n (%)	8 (21.6)
Mycophenolate mofetil, n (%)	3 (8.1)
Cyclophosphamide, n (%)	1 (2.7)
Baricitinib, n (%)	2 (5.4)
Tofacitinib, n (%)	2 (5.4)

anti-MDA5ab: anti-MDA5 antibody; A: peak late; E: peak early; ECG: electrocardiogram; ECHO: echocardiography; F: female; hsTnI: high-sensitivity troponin I; ILD: interstitial lung disease; IVST: inter-ventricular septal thickness; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MMT8: 8-item Manual Muscle Testing; M: male; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RPILD: rapidly progressive ILD; ref: reference range.

Table II. Clinical or relevant serological variables of MDA5-DM patients with LVEF<50% measured by ECHO.

n.	Age/Sex	LVEF (%)	Duration (months)	Cutaneous VAS	Skeletal VAS	Gastrointestinal VAS	Pulmonary VAS	Muscle VAS	Anti-MDA5ab titer (RU/mL)	NT-proBNP (pg/mL)
1	55/F	48	7	5	0	0	4	3	171.8	675
2	43/F	40	29	10	2	0	1	3	169.7	5157
3	25/M	44	2	9	0	0	6	3	150.4	516
4	41/M	45	3	10	0	4	5	7	196	754

anti-MDA5ab: anti-MDA5 antibody; ECHO: echocardiography; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VAS: Visual Analogue Scale.

injecting 0.15 mmol/kg Gd-DTPA using a two-dimensional phase-sensitive inversion-recovery gradient-echo pulse sequence.

Native T1 mapping was performed using an ECG-gated single-shot modified Look-Locker inversion recovery (MOLLI) sequence with a 5(3)3. Post-contrast T1 mapping was performed 15 min after gadolinium administration using MOLLI with a 4(1)3(1)2. T2 mapping images were acquired using the T2-prepared single-shot steady-state free precession technique before the administration of Gd-DTPA. Haematocrit (HCT) was measured within 3 days of CMR scanning.

The extracellular volume (ECV) fraction was analysed semi-automatically using offline software (CVI42; Circle Cardiovascular Imaging, Calgary, Alberta, Canada). The ECV fraction was calculated using pre- and post-gadolinium contrast T1 values of the myocardium and blood pool along with the HCT value (7). Native T1 mapping, T2 mapping, and ECV was measured in 16 American Heart Association segments by delineating the endocardium and epicardium. Based on a previous study, the upper limit of the normal ECV was set at 29.8% (15). Furthermore, the upper limit of normality for native T1 and T2 mapping was established as the 95th percentile of the data obtained from HCs, which were 1040 ms and 52.8 ms, respectively. Myocardial involvement was defined as an abnormality in native T1 mapping, T2 mapping, or ECV.

Statistical analysis

Statistical analyses were performed using IBM SPSS v. 23.0 software (Armonk, NY, USA). Continuous data were presented as mean ± standard deviation or median (interquartile range), whereas categorical variables were expressed as frequencies and percentages. Independent-sample t-tests or Mann-Whitney U-tests were used to compare continuous variables between the groups. The relationship between clinical variables and myocardial involvement was assessed using multivariate logistic regression models. The Wilcoxon signed-rank test or paired-sample t-tests were used to evaluate whether there were significant differences in native T1 and T2 mapping and ECV between the baseline and follow-up measurements. A two-sided *p*-value <0.05 was considered statistically significant.

Table III. CMR parameters in patients with MDA5-DM and HCs.

Parameters	HCs (n=31)	MDA5-DM (n=37)	*p*-value
Age, mean ± SD, years	45.6 ± 13.5	41.6 ± 11.2	NS
Male, n (%)	13 (41.9)	21 (56.8)	NS
LV morphological and functional parameters			
LVEF, %	64.1 ± 4.8	58.9 ± 7.7	0.001
EDVI, mL/m^2	63.0 (53.0, 72.0)	55.0 (48.0, 72.0)	NS
ESVI, mL/m^2	21.0 (20.0, 27.0)	24.0 (17.0, 31.0)	NS
Cardiac index, L/min/m^2	2.7 (2.3, 2.9)	2.8 (2.5, 3.1)	NS
LVMI, g/m^2	56.1 ± 8.8	58.5 ± 12.5	NS
Presence of LGE, n (%)	-	15 (40.5)	-
Mapping parameters			
Native T1 mapping, ms	1004.0 ± 22.9	1045.6 ± 41.5	< 0.001
T2 mapping, ms	47.8 ± 2.3	49.9 ± 3.5	0.007
ECV, %	-	30.08 ± 3.4	-
Elevated ECV, n (%)	-	17 (45.9)	-

CMR: cardiac magnetic resonance; ECV: extracellular volume; EDVI: end-diastolic volume index; ESVI: end-systolic volume index; HCs: healthy controls; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NS: non-significant.

Results

Baseline characteristics of patients with MDA5-DM

This study enrolled 37 (21 male, 16 female) patients diagnosed with MDA5-DM, with a mean age of 41.6±11.2 years. The baseline clinical characteristics of the patients are shown in Table I. In our cohort, three patients (3/37, 8.1%) had chest pain, and nine (9/37, 24.3%) had palpitations. Regarding ECG abnormalities, the incidence of sinus tachycardia and ST-T changes were both 13.5%, and three (8.1%) patients exhibited premature atrial/ventricular contraction. Although all patients exhibited normal LV morphology on ECHO, four patients had decreased LVEF measured by ECHO. As shown in Table II, all four patients had high serum levels of anti-MDA5ab and NT-proBNP, and three had severe cutaneous lesions (Fig. 1). In this study, the majority of patients with RP-ILD were unable to undergo PFTs due to physical limitations. Therefore, only 24 patients with MDA5-DM completed PFTs. The mean values of pulmonary function parameters were as follows: forced vital capacity (FVC) 81.6±17.7%, total lung capacity (TLC) 80±14.3%, and diffusing capacity for carbon monoxide (DLCO) 58.6±16.8%.

CMR findings

Comparisons of CMR parameters between patients with MDA5-DM and HCs are presented in Table III. No sig-

Table IV. Comparison of clinical characteristics between MDA5-DM patients with normal and abnormal CMR.

Variables	CMR-normal patients (n=13)	CMR-abnormal patients (n=24)	*p*-value
Duration, months	7 (1.5, 11)	11 (2.25, 29.75)	NS
Constitutional VAS	1 (1, 2)	3.5 (2, 5)	0.001
Cutaneous VAS	2.85 ± 1.52	6.21 ± 2.28	<0.001
Skeletal VAS	0 (0, 0)	0 (0, 0.25)	NS
Gastrointestinal VAS	0 (0, 1.5)	0 (0, 0)	NS
Muscle VAS	1 (0, 2)	2 (0.25, 3)	NS
Pulmonary VAS	2 (2, 4)	3.5 (2.75, 5.25)	NS
Anti-MDA5ab titre , Ru/mL	77.25 ± 47	139.88 ± 46.53	<0.001
NT-proBNP, pg/mL	34 (25.5, 64)	214..5 (62.25, 568.5)	<0.001

anti-MDA5ab: anti-MDA5 antibody; CMR: cardiac magnetic resonance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NS: non-significant; VAS: Visual Analogue Scale.

nificant differences were observed in EDVI, ESVI, cardiac index, or LVMI between the two groups. However, 15 patients had LGE, and LVEF decreased significantly (58.9±7.7% *vs*. 64.1±4.8%, *p*=0.001) in the MDA5-DM group. Additionally, 64.9% of the patients had abnormalities in native T1 and T2 mapping, or ECV. Patients with MDA5-DM exhibited significantly higher values in native T1 mapping (1045.6±41.5 ms *vs*. 1004.0±22.9 ms, *p*<0.001) and T2 mapping (49.9±3.5 ms *vs*. 47.8±2.3 ms, *p*=0.007) compared to HCs. Simultaneously, elevated ECV was detected in 45.9% of patients. Moreover, CMR mapping parameter analysis of the 16-segment myocardium revealed diffuse myocardial lesions in patients with MDA5-DM (Fig. 2, Supplementary Table S1).

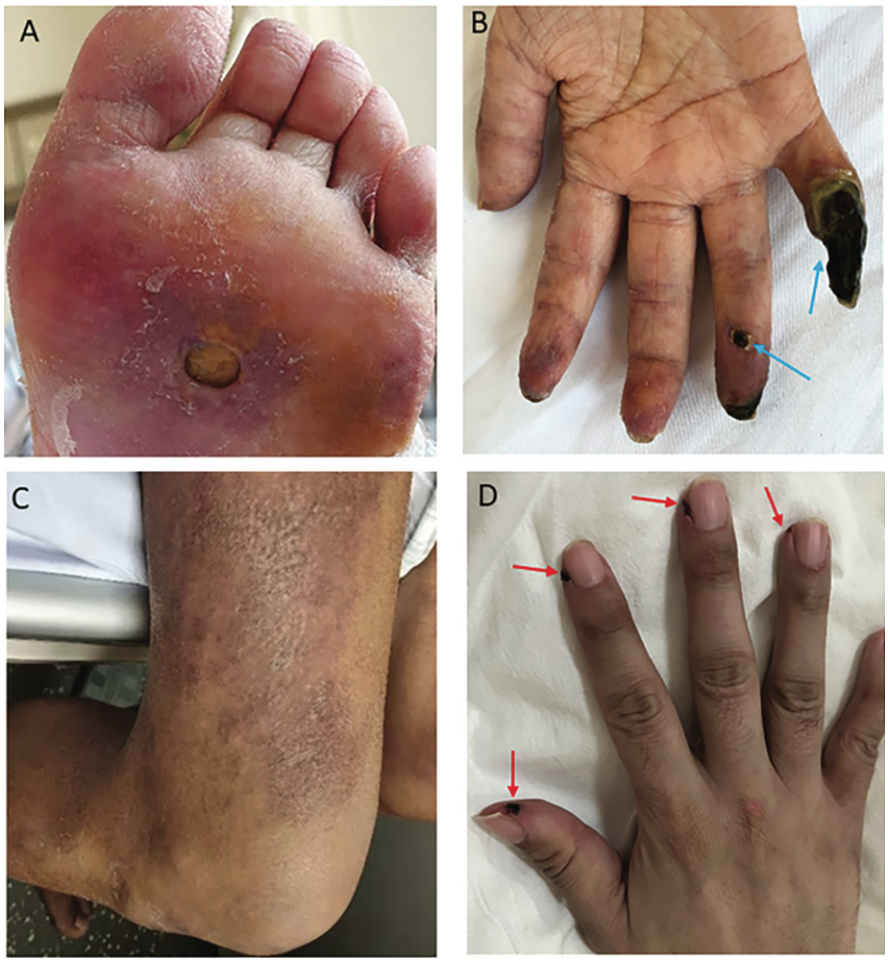

Fig. 1. Cutaneous disease of MDA5-DM. **A**: (patient no. 2): deep ulcers with necrotic crust on the soles. **B**: (patient no. 2): cutaneous ulcerations and necrosis of fingers (blue arrow); **C**: (patient no. 3): Multiple rashes with dyspigmentation on the lower limb. **D**: (patient no. 4): periungual necrosis and ulcerations (red arrow).

Comparison of clinical characteristics between subgroup patients based on CMR mapping parameters

According to CMR mapping parameters, abnormal CMR mapping was detected in 24 (64.9%) patients. Comparisons of clinical characteristics showed that patients with MDA5-DM with abnormal CMR parameters had significantly higher constitutional VAS score (*p*=0.001), cutaneous VAS score (*p*<0.001), serum NT-proBNP level (*p*<0.001) and anti-MDA5ab titre (*p*<0.001) than did those with normal CMR parameters (Table IV). Based on the small sample size and clinical considerations, cutaneous VAS score, serum NT-proBNP level, and anti-MDA5ab titre were included in the multivariate logistic regression analysis. The risk factor for abnormal CMR was cutaneous VAS score (odds ratio: 2.818, 95% confidence interval: 1.088–7.302; *p*=0.033).

Follow-up study

Six patients who underwent CMR review were followed up and analysed. The median follow-up period was 9 (range: 6–14) months. Patients received initial prednisone therapy (1 mg/kg), with a mean initial dose of 55 mg. Additionally, immunotherapies, including cyclophosphamide, cyclosporine, tacrolimus, and mycophenolate mofetil, were prescribed. As depicted in Figure 3, the native T1 mapping [1064.5 ms (1046, 1110.75) *vs*. 1036 ms (1008.5, 1081), *p*=0.046], T2 mapping (52.92±3.68 ms *vs*. 50.27±3.49 ms, *p*=0.024), and ECV values [33.95% (33.4, 36) *vs*. 30.45% (28.33, 30.93), *p*=0.028] showed a significant decline, accompanied by improvement in cutaneous VAS (7.5±2.35 *vs*. 2.33±1.03, *p*=0.027), serum NT-proBNP levels [447 pg/mL (205.5, 1854.75) *vs*. 98.5

pg/mL (45.75, 396), p=0.028] and anti-MDA5ab titres (150.17±33.04 U/mL *vs*. 76.7±24.72 U/mL, p=0.023) after therapy. Representative CMR images are shown in Figure 4.

Discussion

This prospective study investigated cardiac involvement in patients with MDA5-DM. In our cohort, subclinical cardiac involvement was the predominant manifestation and could be detected sensitively using CMR. The subgroup analysis showed that patients with CMR mapping abnormalities had higher constitutional and cutaneous VAS score, serum NT-proBNP level, and anti-MDA5ab titre, compared with those without such abnormalities. Multivariate regression analysis revealed that cutaneous VAS score was the only independent risk factor for predicting abnormal CMR in patients with MDA5-DM. A follow-up study demonstrated that CMR mapping parameters significantly improved after treatment.

MDA5-DM is recognised as a distinct subtype of IIM, characterised by prominent lung and skin involvement and mild or absent myositis. Recently, cardiac involvement in MDA5-DM has received increased attention (16, 17). Zhou *et al*. (18) reported that 15.8% (12/76) of patients with MDA5-DM had myocardial involvement. Additionally, a study on a Japanese cohort detected abnormal cardiac electrical activity and function during the active disease phase (19). Severe cardiac involvement, leading to death, has also been reported (4, 16, 18, 20). In our study, three patients (8.1%) complained of chest pain, and nine (24.3%) had palpitations. Sinus tachycardia and ST-T changes were detected in five patients, and three patients had premature atrial/ventricular contractions. Notably, four patients had decreased LVEF on ECHO, and three of them had severe cutaneous disease. Therefore, most patients were asymptomatic of cardiac involvement and had a normal ECG/ECHO.

In recent years, CMR imaging has emerged as a non-invasive method for the assessment of LV structural and functional parameters. CMR imaging parameters, including native T1 and T2 mapping, as well as ECV, enhance sensitivity for detecting early-stage myocardial impairment. Specifically, native T1 mapping comprehensively assesses oedema, necrosis, and fibrosis, whereas T2 mapping assesses active myocardial inflammation. The ECV is effective in identifying myocardial interstitial fibrosis (7). Therefore, CMR mapping techniques are emerging as quantitative approaches for identifying diffuse myocardial oedema and fibrosis.

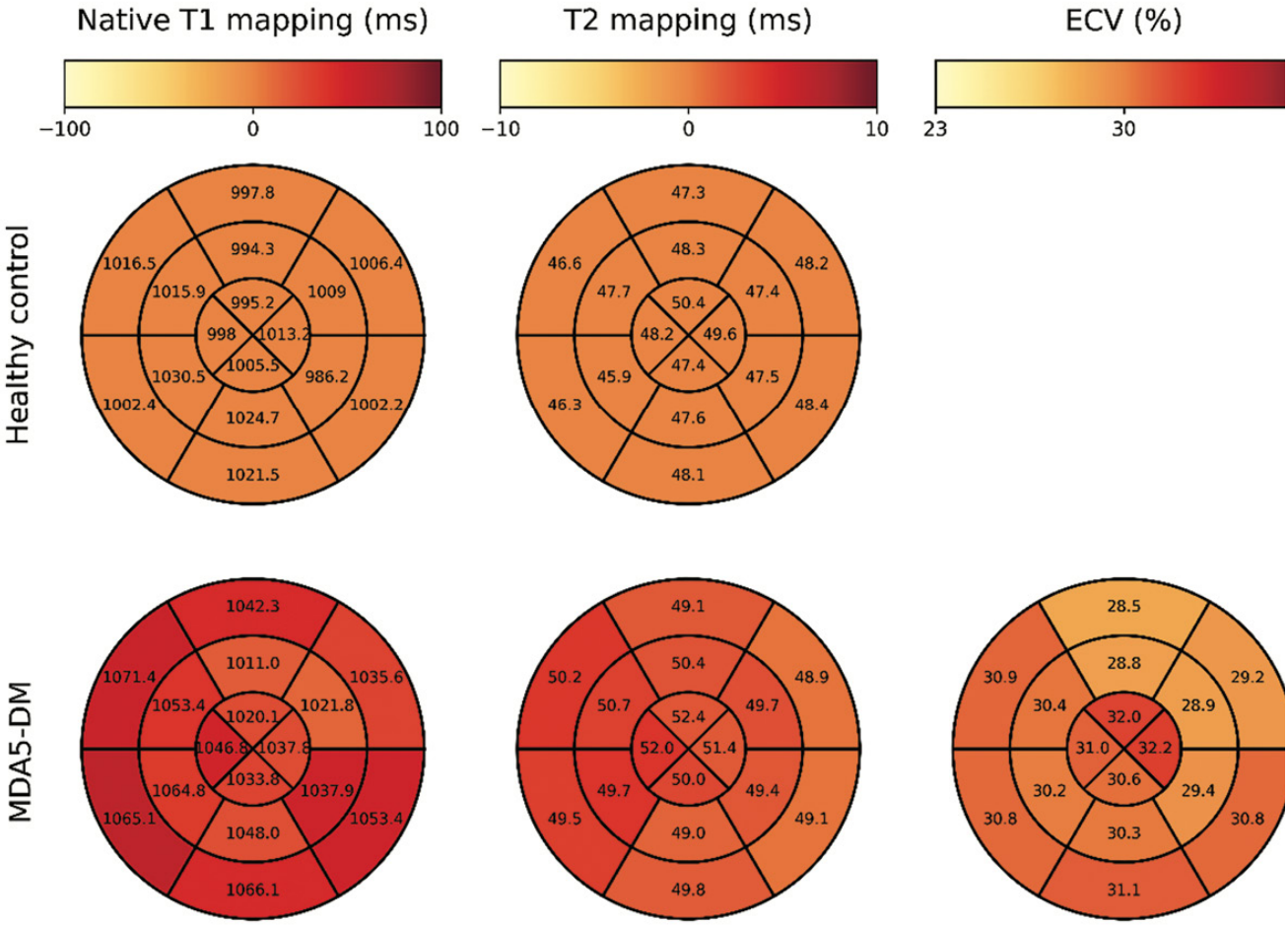

Fig. 2. Bull's eye plots comparing the CMR mapping values of MDA5-DM patients. The value in the middle of each segment represents the average value of this segment. The intensity of each segment colour, relative to that of the HCs, corresponds directly to the magnitude of the mapping parameter value for that particular segment. Regions demonstrating an ECV greater than 29.8% are marked in red.

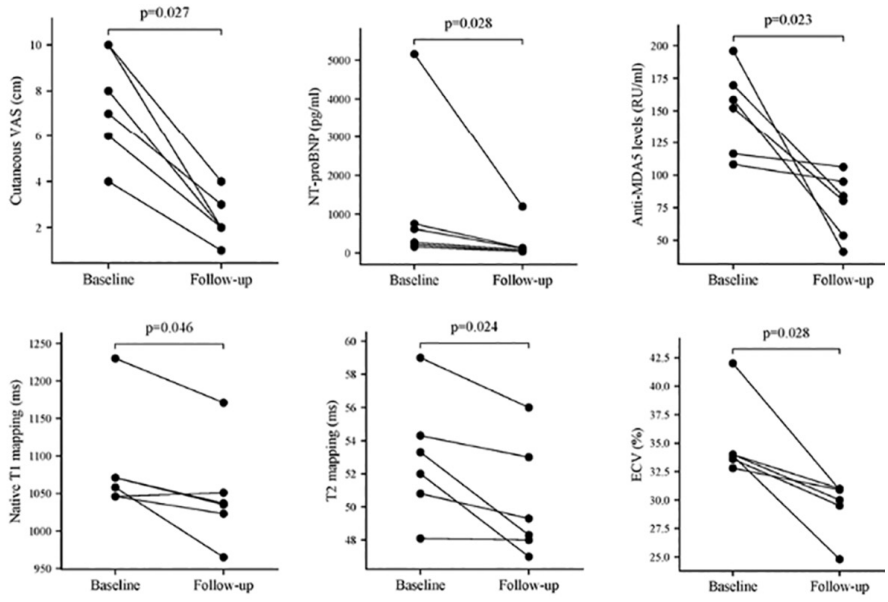

Fig. 3. Clinical data and CMR mapping parameters of follow-up patients with MDA5-DM.

In this study, no significant differences in conventional LV morphology were observed between the patients with MDA5-DM and HCs. However, patients with MDA5-DM exhibited a significant decrease in LVEF, along with a notable increase in native T1 and T2 mapping, compared with HCs. Additionally, 45.9% of the patients showed elevated ECV. These results suggest that CMR imaging, especially CMR mapping parameters, can sensitively detect subclinical cardiac involvement in patients with MDA5-DM. Moreover, the distribution of myocardial damage was found to be diffuse by analysing the CMR mapping parameters of the 16 myocardial segments.

In our cohort, the prevalence of abnormal CMR mapping was 64.9%, indicating that subclinical myocardial damage is common in MDA5-DM. A comparison of clinical characteristics between patients with and without CMR abnormalities suggested that patients with such abnormalities had higher constitutional and cutaneous VAS score, compared with those without. Regarding laboratory findings, NT-proBNP level and anti-MDA5ab titre were significantly higher in patients with abnormal CMR parameters. Previous studies have indicated a close association between the anti-MDA5ab titre and disease activity (17, 21). The difference in anti-MDA5ab titre between the two subgroups suggested that patients with MDA5-DM who exhibit high disease activity were more likely

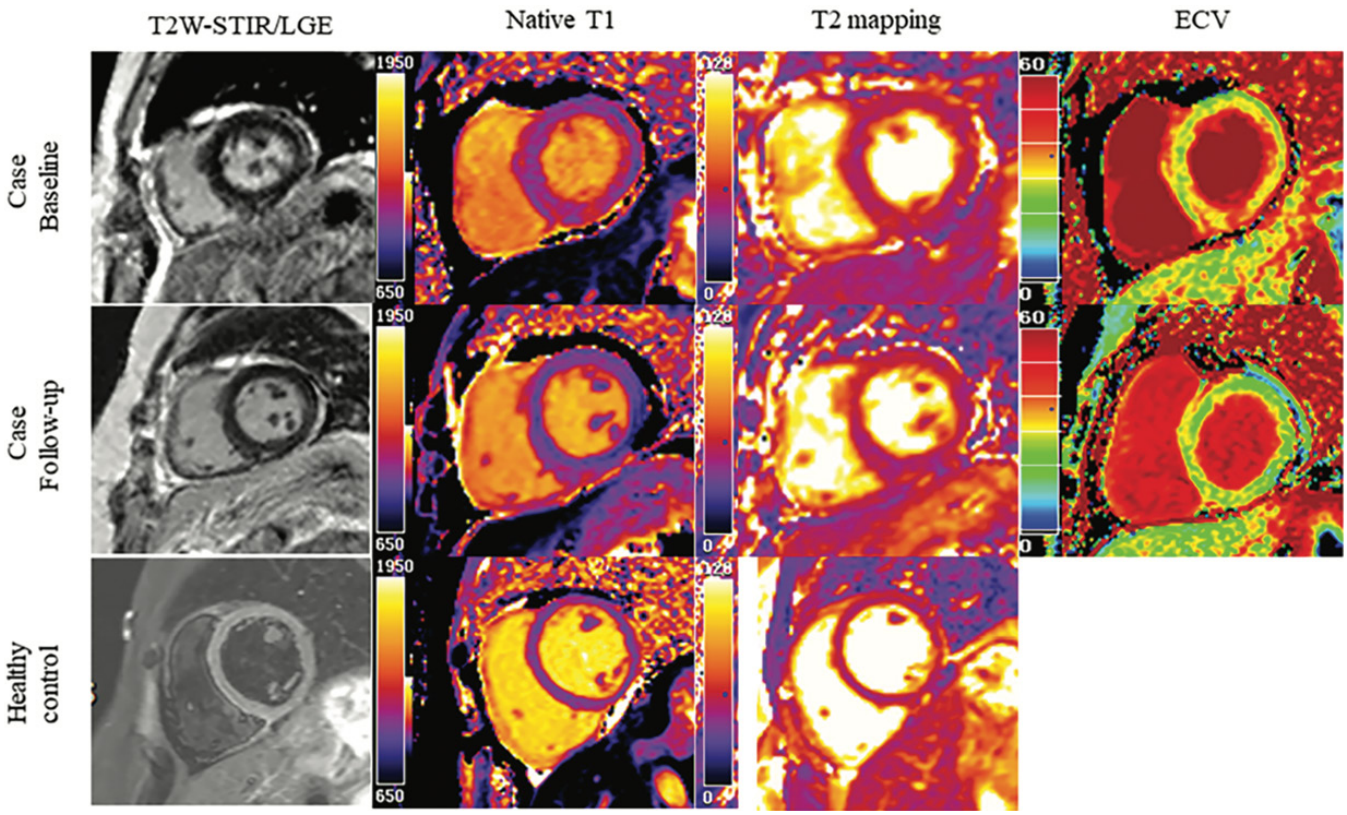

Fig. 4. Representative images of T2W-STIR/ LGE, native T1 mapping, T2 mapping, and ECV in patients with MDA5-DM. Images of a MDA5-DM patient at baseline and subsequent CMR follow-up was obtained, alongside images of a healthy subject (bottom).
ECV: extracellular volume; LGE: late gadolinium enhancement; T2W-STIR: T2-weighted short tau inversion recovery.

to have abnormal CMR parameters. NT-proBNP is widely used as a reliable serum marker for detecting and evaluating heart failure (22). Consistent with previous research result (18), our data showed that serum NT-proBNP level may be a red flag for abnormal CMR in MDA5-DM. Furthermore, logistic regression analysis revealed that cutaneous VAS score was the only independent risk factor that could predict abnormal CMR in patients with MDA5-DM. Therefore, cutaneous lesions appear to be closely correlated with cardiac involvement in MDA5-DM.

Skin lesions are a prominent clinical manifestation of MDA5-DM, including skin ulcerations, palmar papules, alopecia, and calcinosis. Skin ulceration is the most characteristic presentation of MDA5-DM and is less common in other types of dermatomyositis. Several case reports have described patients with prominent cardiac involvement and cutaneous ulcerations (3, 20, 23, 24). Some studies have suggested a close relationship between cutaneous ulcerations and prominent pulmonary diseases, including ILD and recurrent pneumomediastinum (25, 26). Meanwhile, previous research reported that skin ulcer increased the risk of early death for MDA5-DM (27). Therefore, these studies indicate that MDA5-DM patients with serious cutaneous lesions should require more attention. Concerns regarding dermatopathology, interface dermatitis, vasculopathy with infiltration of mononuclear cells, endothelial cell swelling and ballooning, and fibrin deposition in the vessel walls have also been described (28, 29). Cases of vasculitis in ulcerated lesions have been reported (30, 31). Elevated serum levels of endothelial markers (endothelin, thrombomodulin, and plasminogen activator inhibitor) and microvascular injury in lung biopsies suggested underlying systemic vasculopathy in patients with MDA5-DM, which may explain the link between skin lesions and lung involvement (32, 33). Overactivation of the type I interferon (IFN-I) signalling pathway is a well-known feature of MDA5-DM (16). Previous study demonstrated that IFN-I and various type I IFN-inducible genes are overexpressed in the blood, skin, lungs, and muscles of patients with MDA5-DM (34-36). IFN-I can damage endothelial cells by increasing inflammasome activation and impairing vascular repair through deleterious effects on endothelial progenitor cells and circulating myeloid angiogenic cells, which play important roles in vascular repair (37). Therefore, some pathological mechanisms may correlate with skin lesions and cardiac involvement and require further elucidation.

Follow-up of six patients with abnormal CMR findings showed that the CMR parameters (native T1 and T2 mapping and ECV values) significantly decreased, accompanied by an improvement in the cutaneous VAS score, serum NT-proBNP level, and anti-MDA5ab titre. Our data indicate that cardiac involvement in MDA5-DM may improve after treatment with prednisone and immunosuppressants.

This study has certain limitations. First, as a single-centre study, there was an increased risk of selection bias, and the small sample size and only 6 follow-up patients may have impacted the statistical results. Future multicentre studies should include larger sample sizes to enhance the validity of these findings. Second, comparing ECV differences between patients and HCs was not possible because of the absence of enhanced CMR in the HCs group. Third, the function and structure of the right ventricles were not included in our study and require further investigation.

Conclusion

This study sheds light on the high prevalence of subclinical myocardial involvement in patients with MDA5-DM, which can be sensitively detected using CMR mapping parameters. Patients with abnormal CMR mapping were more likely to have higher disease activity and more severe skin lesions. A follow-up study showed that myocardial damage may improve after therapy. Therefore, careful attention should be given to subclinical myocardial involvement in patients with MDA5-DM, particularly those with serious skin lesions.

Acknowledgements

We would like to thank Editage (www.editage.cn) for the English language editing.

References

1. LUNDBERG IE, FUJIMOTO M, VENCOVSKY J *et al*.: Idiopathic inflammatory myopathies. *Nat Rev Dis Primers* 2021; 7(1): 86. https://doi.org/10.1038/s41572-021-00321-x
2. WU W, GUO L, FU Y *et al*.: Interstitial lung disease in anti-MDA5 positive dermatomyositis. *Clin Rev Allergy Immunol* 2021; 60(2): 293-304. https://doi.org/10.1007/s12016-020-08822-5
3. QUINTERO-GONZÁLEZ DC, NAVARRO-BELEÑO K, LÓPEZ-GUTIÉRREZ LV, MUÑOZ-URBANO M, VANEGAS-GARCÍA A-L, MUÑOZ-VAHOS CH: Cardiac involvement in anti-MDA5 dermatomyositis: a case-based review. *Clin Rheumatol* 2022; 42(3): 949-58. https://doi.org/10.1007/s10067-022-06401-x
4. MA X, XU L, LI Y, BU B: Immunotherapy reversed myopathy but not cardiomyopathy in a necrotizing autoimmune myopathy patient with positive anti-SRP and MDA-5 autoantibodies. *BMC Cardiovasc Disord* 2021; 21(1). https://doi.org/10.1186/s12872-021-01900-2
5. SAKURAI N, NAGAI K, TSUTSUMI H, ICHIMIYA S: Anti-CADM-140 antibody-positive juvenile dermatomyositis with rapidly progressive interstitial lung disease and cardiac involvement. *J Rheumatol* 2011; 38(5): 963-64. https://doi.org/10.3899/jrheum.101220
6. LIU X-H, FENG X-J, SHI J-Y *et al*.: The quest for diagnostic approaches of cardiac involvement in polymyositis and dermatomyositis. *Ann Palliat Med* 2020; 9(4): 2256-70. https://doi.org/10.21037/apm-19-650
7. FERREIRA VM, SCHULZ-MENGER J, HOLMVANG G *et al*.: Cardiovascular magnetic resonance in nonischemic myocardial inflammation. *J Am Coll Cardiol* 2018; 72(24): 3158-76. https://doi.org/10.1016/j.jacc.2018.09.072
8. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292(7): 344-47. https://doi.org/10.1056/nejm197502132920706
9. LUNDBERG IE, TJÄRNLUND A, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Arthritis Rheumatol* 2017; 69(12): 2271-82. https://doi.org/10.1002/art.40320
10. HE L, GE Y, LI S *et al*.: Clinical role of bronchoalveolar lavage in dermatomyositis-associated interstitial lung disease. *Rheumatology* 2022; 61(1): 345-54. https://doi.org/10.1093/rheumatology/keab586
11. HUH JW, KIM DS, LEE CK *et al*.: Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. *Respir Med* 2007; 101(8): 1761-69. https://doi.org/10.1016/j.rmed.2007.02.017
12. TRAVIS WD, COSTABEL U, HANSELL DM *et al*.: An Official American Thoracic Society/European Respiratory Society Statement: Update of the international multidisciplinary classification of the idiopathic interstitial

pneumonias. *Am J Respir Crit Care Med* 2013; 188(6): 733-48. https://doi.org/10.1164/rccm.201308-1483ST
13. SULTAN SM, ALLEN E, ODDIS CV *et al*.: Reliability and validity of the myositis disease activity assessment tool. *Arthritis Rheum* 2008; 58(11): 3593-99. https://doi.org/10.1002/art.23963
14. RIDER LG, KOZIOL D, GIANNINI EH *et al*.: Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. *Arthritis Care Res* 2010; 62(4): 465-72. https://doi.org/10.1002/acr.20035
15. MARQUES MD, NAUFFAL V, AMBALE-VENKATESH B *et al*.: Association between inflammatory markers and myocardial fibrosis. *Hypertension* 2018; 72(4): 902-8. https://doi.org/10.1161/hypertensionaha.118.11463
16. LU X, PENG Q, WANG G: Anti-MDA5 antibody-positive dermatomyositis: pathogenesis and clinical progress. *Nat Rev Rheumatol* 2023; 20(1): 48-62. https://doi.org/10.1038/s41584-023-01054-9
17. CAO H, PAN M, KANG Y *et al*.: Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. *Arthritis Care Res* 2012; 64(10): 1602-10. https://doi.org/10.1002/acr.21728
18. ZHOU S, LAI J, WU C *et al*.: Myocardial involvement is not rare in anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis/clinically amyopathic dermatomyositis: a retrospective study. *Front Immunol* 2022; 13. https://doi.org/10.3389/fimmu.2022.928861
19. MATSUO T, SASAI T, NAKASHIMA R *et al*.: ECG Changes through immunosuppressive therapy indicate cardiac abnormality in anti-MDA5 antibody-positive clinically amyopathic dermatomyositis. *Front Immunol* 2022; 12. https://doi.org/10.3389/fimmu.2021.765140
20. PAU-CHARLES I, MORENO PJ, ORTIZ-IBÁÑEZ K *et al*.: Anti-MDA5 positive clinically amyopathic dermatomyositis presenting with severe cardiomyopathy. *J Eur Acad Dermatol Venereol* 2013; 28(8): 1097-102. https://doi.org/10.1111/jdv.12300
21. GONO T, SATO S, KAWAGUCHI 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* 2012; 51(9): 1563-70. https://doi.org/10.1093/rheumatology/kes102
22. BAYES-GENIS A, DOCHERTY KF, PETRIE MC *et al*.: Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: A clinical consensus statement from the Heart Failure Association of the ESC. *Eur J Heart Fail* 2023; 25(11): 1891-98. https://doi.org/10.1002/ejhf.3036
23. KUSHNIR-GRINBAUM D, COHEN-BARAK E, BIEBER A *et al*.: Toxic epidermal necrolysis–like dermatomyositis associated with antimelanoma differentiation antigen 5. *JAAD Case Rep* 2019; 5(1): 91-93. https://doi.org/10.1016/j.jdcr.2018.10.018
24. SHAKSHOUK H, DESCHAINE MA, WETTER DA *et al*.: Do histopathological features correlate with systemic manifestations in dermatomyositis? Analysis of 42 skin biopsy specimens from 22 patients. *J Cutan Pathol* 2022; 49(5): 442-47. https://doi.org/10.1111/cup.14203
25. NARANG NS, CASCIOLA-ROSEN L, LI S, CHUNG L, FIORENTINO DF: Cutaneous ulceration in dermatomyositis: association with anti-melanoma differentiation-associated gene 5 antibodies and interstitial lung disease. *Arthritis Care Res* 2015; 67(5): 667-72. https://doi.org/10.1002/acr.22498
26. LI J, LIU Y, LI Y *et al*.: Associations between anti-melanoma differentiation-associated gene 5 antibody and demographics, clinical characteristics and laboratory results of patients with dermatomyositis: a systematic meta-analysis. *J Dermatol* 2018; 45(1): 46-52. https://doi.org/10.1111/1346-8138.14092
27. LIU L, ZHANG Y, SHU X *et al*.: Predictors of mortality for dermatomyositis patients positive with anti-melanoma differentiation-related gene 5 and optimal treatment. *Clin Exp Rheumatol* 2024; 42(2): 246-52. https://doi.org/10.55563/clinexprheumatol/1vz1p2
28. OKIYAMA N, YAMAGUCHI Y, KODERA M *et al*.: Distinct histopathologic patterns of finger eruptions in dermatomyositis based on myositis-specific autoantibody profiles. *JAMA Dermatol* 2019; 155(9): 1080-82. https://doi.org/10.1001/jamadermatol.2019.1668
29. 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. *J Am Acad Dermatol* 2011; 65(1): 25-34. https://doi.org/10.1016/j.jaad.2010.09.016
30. SHAKSHOUK H, DESCHAINE MA, WETTER DA, DRAGE LA, ERNSTE FC, LEHMAN JS: Clinical and histopathological features of adult patients with dermatomyositis and melanoma differentiation associated-5 autoantibody seropositivity status, as determined by commercially available testing: a retrospective, single-institution comparative cohort study. *Clin Exp Dermatol* 2021; 47(2): 282-88. https://doi.org/10.1111/ced.14870
31. AHMED A, SCARBOROUGH R, GABRIELA R, FERNANDEZ AP, BERGFELD W: Seronegative dermatomyositis presenting with features of anti-MDA5 subtype. *J Cutan Pathol* 2018; 45(11): 851-54. https://doi.org/10.1111/cup.13324
32. FUNAUCHI M, SHIMADSU H, TAMAKI C *et al*.: Role of endothelial damage in the pathogenesis of interstitial pneumonitis in patients with polymyositis and dermatomyositis. *J Rheumatol* 2006; 33(5): 903-6.
33. MAGRO CM, ROSS P, MARSH CB *et al*.: The role of anti-endothelial cell antibody-mediated microvascular injury in the evolution of pulmonary fibrosis in the setting of collagen vascular disease. *Am J Clin Pathol* 2007; 127(2): 237-47. https://doi.org/10.1309/cnqdmhlh2wgkl32t
34. QIAN J, LI R, CHEN Z, CAO Z, LU L, FU Q: Type I interferon score is associated with the severity and poor prognosis in anti-MDA5 antibody-positive dermatomyositis patients. *Front Immunol* 2023; 14: 1151695. https://doi.org/10.3389/fimmu.2023.1151695
35. CASSIUS C, AMODE R, DELORD M *et al*.: MDA5(+) Dermatomyositis is associated with stronger skin type I interferon transcriptomic signature with upregulation of IFN-κ transcript. *J Invest Dermatol* 2020; 140(6): 1276-79.e7. https://doi.org/10.1016/j.jid.2019.10.020
36. JIANG Y, LIU Y, ZHAO Y *et al*.: Mitochondrial morphology and MAVS-IFN1 signaling pathway in muscles of anti-MDA5 dermatomyositis. *Ann Clin Transl Neurol* 2021; 8(3): 677-86. https://doi.org/10.1002/acn3.51311
37. AMBLER WG, KAPLAN MJ: Vascular damage in systemic lupus erythematosus. *Nat Rev Nephrol* 2024; 20(4): 251-65. https://doi.org/10.1038/s41581-023-00797-8