The clinical characteristics of subcutaneous and mediastinal emphysema in anti-melanoma differentiation-associated 5 positive dermatomyositis associated with interstitial lung disease

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Abstract

Objective

To investigate the clinical characteristics of subcutaneous emphysema (SE) and mediastinal emphysema (ME) occurring in patients with anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis associated with interstitial lung disease (anti-MDA5-positive DM-ILD).

Methods

In this retrospective study, a total of 117 anti-MDA5-positive DM-ILD patients were admitted to our hospital. All patients underwent an assessment of autoantibodies, serum ferritin levels, and lung high-resolution CT scans.

Results

In patients with anti-MDA5-positive DM-ILD, the incidence of SE/ME was found to be 11.1%, which was significantly higher compared to patients with anti-synthetase syndrome ($p<0.01$). The mortality rate among anti-MDA5-positive DM-ILD patients with SE/ME was significantly higher than those without SE/ME ($p=0.0022$). There was no statistically significant difference in the occurrence of SE/ME between patients with positive anti-Ro-52 antibodies and those with negative anti-Ro-52 antibodies ($p=0.18$). Patients with higher serum ferritin levels (1000 ng/ml ≤serum ferritin ≤1500 ng/ml) had a higher likelihood of developing SE/ME compared to patients with lower serum ferritin levels (serum ferritin <500 ng/ml) ($p<0.01$). Among 13 anti-MDA5-positive DM-ILD patients with SE/ME, six (46.2%) developed SE/ME within 1 month of being diagnosed and 53.8% of patients underwent positive pressure ventilation prior to the onset of SE/ME.

Conclusion

We found that SE/ME is not uncommon in anti-MDA5-positive DM-ILD and is an important factor associated with poor patient prognosis. The occurrence of SE/ME is correlated with high levels of serum ferritin and is not related to anti-Ro-52 antibodies. Rheumatologists should pay close attention to SE/ME caused by positive pressure ventilation in anti-MDA5-positive DM-ILD patients.

Key words

anti-MDA5-positive dermatomyositis-interstitial lung disease, subcutaneous and mediastinal emphysema, anti-Ro-52 antibodies, serum ferritin, positive pressure ventilation

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Introduction

Dermatomyositis (DM) is an autoimmune disease that primarily affects the skin, skeletal muscles, joints, and lungs. In 2005, Sato *et al*. (1) first detected autoantibodies to a 140-kD polypeptide in patients clinically diagnosed with amyopathic dermatomyositis. Subsequently, in 2009, they further identified this polypeptide as the anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5) (2). The condition of anti-MDA5-positive DM has garnered significant attention due to its poor prognosis and high mortality. Currently, clinical research on anti-MDA5-positive DM primarily focuses on the complication of rapidly progressive interstitial lung disease (RP-ILD), which is a significant cause of mortality in these patients (3, 4). As our understanding of this disease deepens, some scholars have reported that subcutaneous emphysema and mediastinal emphysema are severe complications associated with anti-MDA5-positive DM (5). However, there are no studies on the characteristics of SE/ME in patients with anti-MDA5-positive DM. Therefore, in this study, a retrospective analysis of 117 cases of anti-MDA5-positive DM-ILD from the Department of Rheumatology and Immunology at the Second Affiliated Hospital of Chongqing Medical University was conducted. The aim of this analysis was to summarise the clinical characteristics of anti-MDA5-positive DM-ILD associated with SE/ME. By doing so, it is expected that the understanding of anti-MDA5-positive DM will be further enhanced, and valuable real-world data for future research will be provided.

Methods

From September 2015 to June 2022, a total of 117 anti-MDA5-positive DM-ILD patients and 133 anti-synthetase syndrome (ASSD) -ILD patients, with complete clinical data, were hospitalized at the Second Affiliated Hospital of Chongqing Medical University. The diagnosis of ASSD-ILD (relevant autoantibodies: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ antibodies) and anti-MDA5-positive DM-ILD were based on the 2004 European Neuromuscular Centre (ENMC) classification criteria for idiopathic inflammatory myopathies (6). In accordance with the Declaration of Helsinki, all patients or relatives gave their informed consent to participate and agreed to publication of their data. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

The antisynthetase antibodies, anti-MDA5 antibodies and anti-Ro-52 antibodies were detected using the OMRMUN assay kit (EUROIMMUN, Beijing, China). Serum ferritin levels were measured using the chemiluminescence method with an Access Ferritin kit (Beckman Coulter, Brea, CA, USA, reference range: 11.0–306.8 ng/ml, upper limit 1500 ng/ml). Chest high-resolution computed tomography (HRCT) was performed in all patients to assess subcutaneous and mediastinal emphysema by one experienced radiologist and one experienced respiratory physician. All SE/ME patients were showed the Macklin sign on the HRCT, an air collection adjacent to bronchus and pulmonary vessel.

Grouping: 1. The 117 anti-MDA5-positive DM-ILD patients were divided into two groups based on the occurrence of SE/ME. They were followed up regularly for at least 12 months to understand and analyse their prognosis. 2. The 117 patients were divided into two groups based on the presence or absence of anti-Ro-52 antibodies to determine the correlation between the antibodies and SE/ME. 3. In addition, the patients were divided into three groups based on their serum ferritin levels to investigate the correlation between inflammation and SE/ME.

Statistical analysis

Statistical analyses were conducted using SPSS 19.0 (IBM, Armonk, NY, USA). Data that were consistent with a normal distribution are presented as the mean ± standard deviation. The independent-sample t-test or Fisher's exact test was employed to compare two groups, while multiple comparisons were assessed using the Chi-square test. Kaplan-Meier survival curves were compared using the Log-rank (Mantel-

Cox) test. Statistical significance was defined as $p<0.05$.

Results

Basic information

The average age of the 133 patients diagnosed with ASSD-ILD was 53.08±7.01 years, and the ratio of males to females was 1:1.77. A total of 11 patients underwent non-invasive ventilation or invasive mechanical ventilation, but no instances of subcutaneous and mediastinal emphysema were observed among ASSD-ILD patients. Additionally, a total of 117 patients diagnosed with anti-MDA5-positive DM-ILD were included, who had an average age of 51.09±13.59 years. The gender distribution in this group was 1 male to 1.93 females. Among these patients, 13 individuals developed subcutaneous and mediastinal emphysema, resulting in an incidence rate of 11.1%, which was significantly higher compared to the ASSD-ILD group ($p<0.01$). All patients received treatment with steroids and immunosuppressive agents. In the ASSD-ILD group, there was significantly higher utilisation of cyclophosphamide and methotrexate compared to the anti-MDA5-positive DM-ILD group ($p=0.03$ and $p<0.01$, respectively). Conversely, the utilisation of tacrolimus and cyclosporine was higher in the anti-MDA5-positive DM group compared to the ASSD-ILD group ($p<0.01$) (Table I).

Table I. General information on133 anti-synthetase syndrome and 117 anti-MDA5-positive DM patients.

	Anti-synthetase syndrome (n=133)	Anti-MDA5-positive DM (n=117)	*p*-value
Male	48	40	0.79
Female	85	77	0.79
Age	53.08 ± 7.01	51.09 ± 13.59	0.14
Steroid pulse	29 (21.8%)	16 (13.7%)	0.10
Prednisolone	133 (100%)	117 (100%)	>0.99
IVIG	41 (30.8%)	47 (40.2%)	0.14
Cyclophosphamide	102 (76.7%)	74 (63.2%)	0.03
Mycophenolate mofetil	18 (13.5%)	9 (7.7%)	0.16
Tacrolimus	3 (2.3%)	52 (44.4%)	<0.01
Cyclosporine	0	7 (6.0%)	<0.01
JAK inhibitor	0	2 (1.7%)	0.22
Methotrexate	57 (42.9%)	9 (7.7%)	<0.01
SE/ME	0	13	<0.01

Steroid pulse: methylprednisolone 500 mg daily for 3 days; IVIG: intravenous immunoglobulin; JAK: Janus kinase; SE/ME: subcutaneous emphysema and mediastinal emphysema.

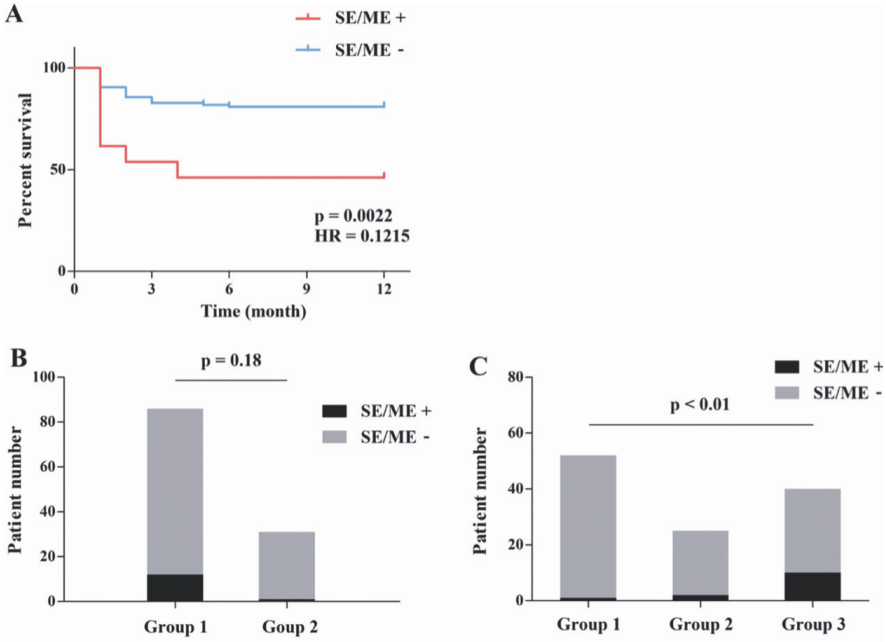

Fig. 1. The clinical characteristics of SE/ME in anti-MDA5-positive DM. **(A)** Survival curves for the anti-MDA5-positive DM with SE/ME (red, n=13) and without SE/ME (blue, n=104), ($p=0.0022$, hazard ratio = 0.1215). **(B)** Relationship between SE/ME and anti-Ro-52 antibodies. In group 1, test for anti-Ro-52 antibodies were positive. (n=86). In group 2, test for anti-Ro-52 antibodies were negative. (n=31). ($p=0.18$). **(C)** Relationship between SE/ME and serum ferritin. Group 1: serum ferritin <500 ng/ml (n=52), Group 2: 500 ng/ml ≤serum ferritin <1000 ng/ml (n=25), and Group 3: 1000 ng/ml ≤serum ferritin ≤1500 ng/ml (n=40).
SE/ME +: anti-MDA5-positive DM with subcutaneous emphysema and mediastinal emphysema; SE/ME -: anti-MDA5-positive DM without subcutaneous emphysema and mediastinal emphysema.

Survival analysis of anti-MDA5-positive DM-ILD patients

The 117 patients diagnosed with anti-MDA5-positive DM-ILD were divided into two distinct groups based on the presence or absence of subcutaneous and mediastinal emphysema (SE/ME). Among 104 anti-MDA5-positive DM-ILD patients who did not exhibit SE/ME, a total of 20 patients (19.2%) died, with all fatalities occurring within 6 months of diagnosis (Blue). On the other hand, among 13 anti-MDA5-positive DM-ILD patients who developed SE/ME, seven patients (53.8%) died. It is worth noting that within this subset, five patients (71.4%) passed away within 1 month following the onset of SE/ME. Additionally, the remaining two patients died at 2 and 4 months, respectively, after the occurrence of SE/ME (Red). The mortality rate among anti-MDA5-positive DM-ILD patients with SE/ME was significantly higher than those without SE/ME. Kaplan-Meier survival curves are presented in Figure 1A and the Log-rank (Mantel-Cox) test showed a statistically significant difference in survival ($p<0.01$).

Relationship between SE/ME and anti-Ro52 antibodies

The 117 anti-MDA5-positive DM-ILD patients were divided into two groups based on the presence or absence of anti-Ro-52 antibodies. The results showed that among the 86 patients who tested positive for anti-Ro-52 antibodies, a total of 12 patients (14.0%) developed SE/

ME (Group 1). Among the 31 patients who tested negative for anti-Ro-52 antibodies, one (3.2%) experienced SE/ME (Group 2). There was no statistically significant difference between the two groups (p=0.18) (Fig. 1B).

Relationship between SE/ME and serum ferritin

The 117 anti-MDA5-positive DM-ILD patients were divided into three groups based on their serum ferritin levels. In Group 1, 52 anti-MDA5-positive DM-ILD patients with a low serum ferritin level (serum ferritin <500 ng/ml), only one patient developed SE/ME. Two anti-MDA5-positive DM-ILD patients developed SE/ME in Group 2 (500 ng/ml ≤serum ferritin <1000 ng/ml, n=25). Group 3 comprised 40 anti-MDA5-positive DM-ILD patients with high level of serum ferritin (1000 ng/ml ≤ serum ferritin ≤1500 ng/ml), among these individuals, a total of 10 patients developed SE/ME. The number of anti-MDA5-positive DM-ILD patients who developed SE/ME in Group 3 was significantly higher than that in Group 1 (p<0.01) (Fig. 1C).

Clinical data of anti-MDA5-positive DM-ILD patients with SE/ME

In our analysis of 13 anti-MDA5-positive DM-ILD patients who experienced SE/ME, we found that six (46.2%) developed SE/ME within 1 month of being diagnosed with anti-MDA5-positive DM-ILD, indicating a rapid progression. We further investigated potential factors associated with the occurrence of SE/ME in anti-MDA5-positive DM-ILD patients. Unexpectedly, seven patients (53.8%) underwent non-invasive ventilation or invasive mechanical ventilation before the onset of SE/ME, one patient underwent excision of lung lesions under thoracoscopy prior to SE/ME, and four patients experienced spontaneous SE/ME. With regard to prognosis, 7 patients eventually died due to their inability to be weaned off the ventilator. Other patients experienced relief through high-flow oxygen therapy, and 2 patients had their subcutaneous emphysema evacuated by puncturing the skin and manually mobilizing air through the puncture holes. The average recovery time was 9.5±5.2 weeks (Table II).

Discussion

Since the discovery of anti-MDA5 antibodies by Japanese researchers, the poor prognosis of anti-MDA5-positive DM, often associated with RP-ILD, has received increasing clinical attention. However, in addition to ILD, subcutaneous and mediastinal emphysema as complications also pose a significant threat to the life and health of anti-MDA5-positive DM patients. Therefore, by summarizing and analysing the clinical characteristics of SE/ME in anti-MDA5-positive DM-ILD patients, we aim to deepen our understanding of this disease.

Firstly, our single-centre data revealed that compared to ASSD-ILD patients, anti-MDA5-positive DM-ILD patients were more prone to developing SE/ME, with an incidence rate as high as 11.1%. This highlights the variability of SE/ME among different subtypes of inflammatory myopathies. We consider that this is partly associated with a higher propensity for diffuse alveolar injury in anti-MDA5-positive DM, which is distinct from ASSD. On the other hand, it may also be related to different pathophysiological pathways involved in the onset of the disease. Studies have shown that interferon-I signalling is enhanced in anti-MDA5-positive DM, significantly higher than in other types of DM (7). But we should point out that it is currently unknown whether there is a correlation between interferon-I signalling and the occurrence of SE/ME, further research is needed to confirm this view. The differences among various subtypes of inflammatory myopathies are also evident in their treatment approaches. We observed that ASSD-ILD patients tend to use cyclophosphamide and methotrexate more frequently, while anti-MDA5-positive DM-ILD patients are inclined to use tacrolimus and cyclosporine. Bueno *et al*. also explicitly stated that the combination of glucocorticoids and calcineurin antagonists is the preferred choice in anti-MDA5-positive DM (8). Therefore, based on the above, we would like to emphasise that although DM shares some common features, such as heliotrope rash, Gottron sign, V-sign, muscle weakness, and ILD, it is crucial for us in our clinical practice to identify the distinct complications associated with different types of DM and adopt specific treatment strategies accordingly.

The survival curve clearly demonstrated that the mortality rate of patients with anti-MDA5-positive DM-ILD who developed SE/ME was significantly higher compared to those who did not experience SE/ME. In fact, a staggering 71.4% of patients died within one month of SE/ME occurrence. These shocking findings suggest a high incidence of SE/ME in anti-MDA5-positive DM-ILD. SE/ME is a complication that cannot be overlooked due to its rapid progression and severe implications for the prognosis of anti-MDA5-positive DM-ILD patients.

Our previous research indicated that anti-MDA5-positive DM-ILD patients who were positive for anti-Ro-52 antibodies were more prone to developing RP-ILD (9) and more susceptible to pulmonary oxidative stress (10). Xu *et al*. also confirmed a higher mortality rate among anti-MDA5-positive DM patients who were positive for anti-Ro-52 antibodies (11). These findings suggest that anti-Ro-52 antibodies play a significant role in anti-MDA5-positive DM. However, the results of this study did not demonstrate a statistically significant difference in the occurrence of SE/ME between patients who were positive or negative for anti-Ro-52 antibodies. It might be related to the small sample size of our centre. Nevertheless, it is worth noting that of the 13 cases of SE/ME in anti-MDA5-positive DM-ILD patients, 12 cases (92.3%) were positive for anti-Ro-52 antibodies. Therefore, we should pay close attention to patients who are positive for both anti-Ro-52 antibodies and anti-MDA5 antibodies, and further validation will be conducted through long-term follow-up.

Elevated serum ferritin is a significant characteristic of anti-MDA5-positive DM with RP-ILD, often indicating more severe pulmonary involvement (12). Takahisa *et al*. (13) even suggested that anti-MDA5-positive DM may be a type of macrophage activa-

Table II. Clinical information of 13 anti-MDA5-positive DM patients with SE/ME.

No.	Sex/age	Anti-Ro-52 antibody	Serum ferritin	Stage 1 (week)	Potential triggers	The duration of assisted ventilation before the development of SE/ME (day)	Positive end-expiratory pressure (cmH_2O)	Treatment	Treatment after SE/ME	Stage 2 (week)
1	M/46	+	1327.7	8	Spontaneous	-	-	Steroid pulse+PSL +IVIG+CYC	High-flow nasal oxygen	17
2	M/58	+	1118.5	29	Excision of lung lesions under thoracoscopy	2	-	Steroid pulse+PSL +CYC+MTX	High-flow nasal oxygen	6
3	F/63	+	≥1500	1	Invasive mechanical ventilation	2	8	Steroid pulse+PSL +CYC+IVIG	Unable to be weaned off the ventilator	dead
4	M/48	+	≥1500	1	Non-invasive ventilation	9	5 - 9	Steroid pulse+PSL +IVIG+CYC	Unable to be weaned off the ventilator	dead
5	M/46	+	879.6	2	Electronic laryngoscope	-	-	Steroid pulse+PSL +IVIG+CSA+CYC	High-flow nasal oxygen	4
6	M/66	-	135.8	1	Spontaneous	-	-	Steroid pulse+PSL +CYC+CSA+IVIG	High-flow nasal oxygen	5
7	M/46	+	≥1500	6	Non-invasive ventilation	2	5	PSL+CYC+IVIG	Change to high-flow nasal oxygen and puncture the skin and manual mobilisation of air through the puncture holes.	13
8	M/84	+	834.3	1	Non-invasive ventilation	4	5 - 11	PSL+IVIG	Unable to be weaned off the ventilator	dead
9	F/53	+	1138.2	1	Non-invasive ventilation	3	5 - 6	PSL+IVIG	Unable to be weaned off the ventilator	dead
10	F/64	+	1105.2	6	Invasive mechanical ventilation	5	5 - 6	PSL+IVIG	Unable to be weaned off the ventilator	dead
11	M/57	+	≥1500	5	Invasive mechanical ventilation	8	5 - 7	PSL+IVIG	Unable to be weaned off the ventilator	dead
12	F/52	+	1209.1	47	Spontaneous	-	-	PSL+TAC+CYC	High-flow nasal oxygen, puncture the skin and manual mobilisation of air through the puncture holes.	12
13	F/59	+	≥1500	18	Spontaneous	-	-	PSL+CYC	Unable to be weaned off the ventilator	dead

Stage 1: The time from diagnosis to the onset of SE/ME.
Stage 2: The time from the onset of SE/ME to recovery.
Steroid pulse: methylprednisolone 500mg daily for 3 days; PSL: prednisolone 40mg daily; IVIG: intravenous immunoglobulin; CYC: cyclophosphamide; CSA: cyclosporine; TAC: tacrolimus.

tion syndrome primarily affecting the lungs. In our study, we grouped 117 anti-MDA5-positive DM-ILD patients based on different levels of serum ferritin and found that the number of patients with SE/ME was significantly higher in the group with serum ferritin levels ranging from 1000 ng/ml to 1500 ng/ml compared to those with serum ferritin levels below 500 ng/ml, confirming the close association between the occurrence of SE/ME and a heightened inflammatory state in anti-MDA5-positive DM-ILD.

However, there is currently no definitive research on how the aforementioned abnormal serological markers affect the occurrence of SE/ME. This prompted us to conduct a detailed analysis of 13 patients with anti-MDA5-positive DM-ILD accompanied by SE/ME. Interest-

ingly, we found that only 4 patients had spontaneous SE/ME, while a significant 53.8% of patients had undergone positive pressure ventilation before the onset of SE/ME. Thus, we need to be highly vigilant regarding the development of subcutaneous and mediastinal emphysema caused by mechanical ventilation in anti-MDA5-positive DM-ILD patients. When diffuse alveolar injury occurs and alveolar rupture ensues, air can travel along the bronchovascular sheath towards the mediastinum or along the cervical fascia into the subcutaneous tissue, ultimately leading to SE and ME. The causes of SE/ME can be spontaneous or traumatic, and positive pressure ventilation is one of the common causes.

Currently, extensive research has provided us with a good understanding of the lung manifestations in anti-MDA5-positive DM. Firstly, lung pathological biopsy has revealed widened alveolar septa, hyperplasia of interstitial fibrous tissue, lymphocyte infiltration (14), and strong expression of immunoglobulin and C3 (15), indicating diffuse alveolar injury. Second, it is well known that non-specific interstitial pneumonia (NSIP) and organising pneumonia (OP) are the primary histopathological patterns observed in anti-MDA5-positive DM-ILD. In the presence of pulmonary interstitial lesions, pulmonary compliance is significantly reduced (16). Lastly, anti-MDA5-positive DM can involve respiratory muscles, ultimately leading to respiratory failure (17). All these factors are considered important causes of subcutaneous and mediastinal emphysema caused by positive pressure ventilation.

Since the outbreak of COVID-19, scholars have pointed out the similarities between COVID-19 and anti-MDA5-positive DM, including aspects such as RP-ILD, elevated serum ferritin levels, decreased lymphocyte count, and more (18, 19). Similarly, researchers also observed the occurrence of pneumothorax, pneumomediastinum and SE caused by positive pressure ventilation in COVID-19 patients with diffuse lung damage (20-22). Therefore, the treatment of severe anti-MDA5-positive DM-ILD patients poses a serious challenge.

When SE/ME occurs in anti-MDA5-positive DM-ILD patients, it is necessary to take proactive treatment measures. Based on experience at our centre, the following approaches are recommended: 1) Actively control anti-MDA5-positive DM-ILD to achieve prompt relief or a state of low disease activity. 2) Minimise unnecessary invasive procedures such as needle biopsy of lung or thoracentesis. 3) Minimise the use of mechanical ventilation as much as possible, provided high-flow oxygen therapy can maintain adequate patient oxygenation. 4) For some critical patients, symptom relief may be achieved by puncturing the skin and manually mobilising air through the puncture holes.

We should also point out the limitations of this retrospective study. The exploration of potential mechanisms in this study were lacking. Besides, we only analysed anti-MDA5-positive DM-ILD patients of our single centre design, which might limit the generalisability of the findings to a certain extent. Finally, we explored the clinical characteristics of SE/ME only in anti-MDA5-positive DM, which may not well reflect the characteristic of SE/ME in other types of inflammatory myopathies.

In conclusion, this study examined the clinical characteristics of subcutaneous and mediastinal emphysema in anti-MDA5-positive DM-ILD, deepening our understanding of the disease. Furthermore, the study provides relevant information for future clinical practice and serves as a reliable basis for further research.

References

1. SATO S, HIRAKATA M, KUWANA M *et al.*: Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum* 2005; 52(5): 1571-6. https://doi.org/10.1002/art.21023
2. SATO S, HOSHINO K, SATOH 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 Rheum* 2009; 60(7): 2193-200. https://doi.org/10.1002/art.24621
3. SO J, SO H, WONG VT *et al.*: Predictors of rapidly progressive interstitial lung disease and mortality in patients with autoantibodies against melanoma differentiation-associated protein 5 dermatomyositis. *Rheumatology* (Oxford) 2022; 61(11): 4437-44. https://doi.org/10.1093/rheumatology/keac094
4. DOURADO E, BOTTAZZI F, CARDELLI C *et al.*: Idiopathic inflammatory myopathies: one year in review 2022. *Clin Exp Rheumatol* 2023; 41(2): 199-213. https://doi.org/10.55563/clinexprheumatol/jof6qn
5. ABE K, FURUTA S, KOBAYASHI Y *et al.*: Prognosis of spontaneous pneumomediastinum occurring in dermatomyositis or polymyositis patients with interstitial lung disease according to antimelanoma differentiation-associated gene 5 antibody status: a retrospective cohort study. *RMD Open* 2023; 9(1): e002770. https://doi.org/10.1136/rmdopen-2022-002770
6. HOOGENDIJK JE, AMATO AA, LECKY BR *et al.*: 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis. *Neuromuscul Disord* 2004; 14(5): 337-45. https://doi.org/10.1016/j.nmd.2004.02.006
7. NOMBEL A, FABIEN N, COUTANT F: Dermatomyositis with anti-MDA5 antibodies: bioclinical features, pathogenesis and emerging therapies. *Front Immunol* 2021; 12: 773352. https://doi.org/10.3389/fimmu.2021.773352
8. ROMERO-BUENO F, DIAZ DEL CAMPO P, TRALLERO-ARAGUÁS E *et al.*: Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin *Arthritis Rheum* 2020; 50(4): 776-90. https://doi.org/10.1016/j.semarthrit.2020.03.007
9. HUANG W, REN F, WANG Q *et al.*: Clinical features of thirty-two patients with anti-melanoma differentiation-associated gene 5 antibodies. *Clin Exp Rheumatol* 2019; 37(5): 803-7.
10. HUANG W, CHEN D, WANG Z *et al.*: Evaluating the value of superoxide dismutase in anti-MDA5-positive dermatomyositis associated with interstitial lung disease. *Rheumatology* (Oxford) 2023; 62(3): 1197-203. https://doi.org/10.1093/rheumatology/keac429
11. XU A, YE Y, FU Q *et al.*: Prognostic values of anti-Ro52 antibodies in anti-MDA5-positive clinically amyopathic dermatomyositis associated with interstitial lung disease. *Rheumatology* (Oxford) 2021; 60(7): 3343-51. https://doi.org/10.1093/rheumatology/keaa786
12. GONO T, KAWAGUCHI Y, HARA M *et al.*: Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. *Rheumatology* (Oxford) 2010; 49(7): 1354-60. https://doi.org/10.1093/rheumatology/keq073
13. 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* (Oxford) 2012; 51(9): 1563-70. https://doi.org/10.1093/rheumatology/kes102
14. CHEN X, JIANG W, JIN Q *et al.*: Clinical, radiological and pathological features of anti-MDA5 antibody-associated interstitial lung disease. *RMD Open* 2023; 9(2): e003150. https://doi.org/10.1136/rmdopen-2023-003150

15. ZAIZEN Y, OKAMOTO M, AZUMA K *et al*.: Enhanced immune complex formation in the lungs of patients with dermatomyositis. *Respir Res* 2023; 24(1): 86. https://doi.org/10.1186/s12931-023-02362-0
16. YAMAZAKI H, FUJIMOTO K: A new noninvasive method for measurement of dynamic lung compliance from fluctuations on photoplethysmography in respiration. *J Appl Physiol (1985)* 2021; 130(1): 215-25. https://doi.org/10.1152/japplphysiol.00295.2020
17. GRIGNASCHI S, MONGODI S, ALFONSI E *et al*.: Respiratory failure due to concomitant interstitial lung disease and diaphragmatic involvement in a patient with anti-MDA5 dermatomyositis: a case report. *Clin Exp Rheumatol* 2022; 134(5): 121-3. https://doi.org/10.55563/clinexprheumatol/0u7vdc
18. DE LORENZIS E, NATALELLO G, GIGANTE L, VERARDI L, BOSELLO SL, GREMESE E: What can we learn from rapidly progressive interstitial lung disease related to anti-MDA5 dermatomyositis in the management of COVID-19? *Autoimmun Rev* 2020; 19(11): 102666. https://doi.org/10.1016/j.autrev.2020.102666
19. CAVAGNA L, FERRO F, ZANFRAMUNDO G, LA ROCCA G, PUXEDDU I: Idiopathic inflammatory myopathies and COVID-19: an intriguing liaison? *Clin Exp Rheumatol* 2023; 41(2): 217-20. https://doi.org/10.55563/clinexprheumatol/njaff0
20. VAZZANA N, OGNIBENE S, DIPAOLA F: Pneumomediastinum and subcutaneous emphysema after noninvasive ventilation in a COVID-19 patient. *Adv Respir Med* 2020; 88(5): 466-7. https://doi.org/10.5603/ARM.a2020.0141
21. SETHI SM, AHMED AS, HANIF S, AQEEL M, ZUBAIRI ABS: Subcutaneous emphysema and pneumomediastinum in patients with COVID-19 disease; case series from a tertiary care hospital in Pakistan. *Epidemiol Infect* 2021; 149: e37. https://doi.org/10.1017/S095026882100011X
22. GUVEN BB, ERTURK T, KOMPE Ö, ERSOY A: Serious complications in COVID-19 ARDS cases: pneumothorax, pneumomediastinum, subcutaneous emphysema and haemothorax. *Epidemiol Infect* 2021; 149: e137. https://doi.org/10.1017/S0950268821001291