The clinical characteristics of pharyngeal and laryngeal lesions in anti-MDA5-positive dermatomyositis patients

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Abstract

Objective

To investigate the clinical characteristics of pharyngeal and laryngeal lesions in patients with anti-melanoma differentiation-associated gene 5 antibodies-positive dermatomyositis (anti-MDA5-positive DM).

Methods

Serological indicators of 131 anti-MDA5-positive DM patients were analysed. All 35 patients with pharyngeal and laryngeal symptoms underwent electronic laryngoscopy examinations.

Results

Pharyngeal and laryngeal symptoms were observed in 26.7% of anti-MDA5-positive DM patients. Low levels of haemoglobin, albumin, prealbumin, high-density lipoprotein and rapidly progressive interstitial lung disease mainly appeared in patients with pharyngeal and laryngeal involvement compared to those without involvement. However, no significant difference in mortality was found between the two groups. The number of patients with pharyngeal and laryngeal involvement was significantly higher in anti-Ro-52 antibody-positive patients than in anti-Ro-52 antibody-negative patients. Patients with higher serum ferritin levels (1000 ng/ml ≤ serum ferritin ≤1500 ng/ml) were more likely to develop pharyngeal and laryngeal involvement compared to those with lower serum ferritin levels (serum ferritin <500 ng/ml). Electronic laryngoscopy examinations effectively assisted rheumatologists in assessing the conditions of the pharyngeal mucosa, arytenoid area, epiglottis, and vocal cords. Some patients also presented with rare lesions such as pharyngeal posterior wall fistulas, epiglottic ulcers, and vocal cord white lesions.

Conclusion

1. Pharyngeal and laryngeal lesions are not uncommon in anti-MDA5-positive DM, these patients have poorer nutritional status and more severe lung lesions; 2. Positive anti-Ro-52 antibodies and high serum ferritin levels are closely associated with pharyngeal and laryngeal involvement in anti-MDA5-positive DM; 3. Electronic laryngoscopy plays a crucial role in the diagnosis and evaluation of pharyngeal and laryngeal conditions.

Key words

anti-MDA5-positive DM, pharyngeal and laryngeal lesions, anti-Ro-52 antibodies, serum ferritin, electronic laryngoscopy

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Received on September 20, 2024; accepted in revised form on November 4, 2024.

Funding: this work was supported by:
the National Natural Science Foundation of China, grant no. 81771738;
the Talents Program of Chongqing, grant no. cstc2022ycjh-bgzxm0139;
the Program for Youth Innovation in Future Medicine, Chongqing Medical University, grant no. W0197.

Competing interests: none declared.

Introduction

Dermatomyositis is an autoimmune disease that primarily affects the skin, muscles, and lungs. Since the discovery of anti-melanoma differentiation-associated gene 5 antibody by Japanese scholars (1, 2), anti-MDA5-positive DM has garnered widespread attention due to its high mortality rate. Undoubtedly, the pulmonary lesions in anti-MDA5-positive DM are the primary focus of assessment for rheumatologists. The presence of rapidly progressive interstitial lung disease (RP-ILD) (3) or subcutaneous emphysema (4)often indicates an extremely poor prognosis for patients. Consequently, the extrapulmonary manifestations of anti-MDA5-positive DM may be overlooked to some extent. In our clinical practice, we have observed that anti-MDA5-positive DM patients are often troubled by pharyngeal and laryngeal symptoms, such as pharyngalgia, dysphagia, and hoarseness. However, there is no systematic research on the characteristics of pharynx and larynx lesions in anti-MDA5-positive DM patients. Accordingly, this study retrospectively analysed 131 anti-MDA5-positive DM patients from the Department of Rheumatology and Immunology at the Second Affiliated Hospital of Chongqing Medical University. The clinical characteristics of anti-MDA5-positive DM associated with pharynx and larynx lesions were investigated to enhance the understanding of this disease and provide valuable real-world data for future research.

Method

From September 2015 to August 2024, 131 anti-MDA5-positive DM patients were hospitalized at the Second Affiliated Hospital of Chongqing Medical University, with complete hospitalisation data. The diagnosis of anti-MDA5-positive DM was based on the European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups (5). In accordance with the Declaration of Helsinki, all patients or relatives provided informed consent to participate and agreed to the publication of their data. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

Pharyngeal and laryngeal symptoms included pharyngalgia, dysphagia (difficulty swallowing, choking while drinking), and hoarseness. The above symptoms caused by gastroesophageal reflux were excluded. All patients presenting with pharyngeal and laryngeal symptoms underwent electronic laryngoscopy examinations, which were evaluated by an experienced otolaryngologist. Haemoglobin, albumin, prealbumin, and blood lipids were detected. The EUROIMMUN assay kit was used to detect anti-MDA5 antibodies and anti-Ro-52 antibodies (EUROIMMUN, Beijing, China). Serum ferritin levels were measured by chemiluminescence method using an Access Ferritin kit (Beckman Coulter, Brea, CA, USA, reference range: 11-306.8 ng/ml, upper limit: 1500 ng/ml). All patients underwent high-resolution computed tomography of the lungs before and after treatment to assess interstitial lung disease (ILD) or rapidly progressive ILD (RP-ILD) by one experienced radiologist and one experienced respiratory physician.

Grouping: (1) The 131 anti-MDA5-positive DM patients were divided into two groups based on the presence or absence of pharyngeal and laryngeal involvement. Serological indicators and prognosis were analysed. (2) Patients were divided into two groups based on the presence or absence of anti-Ro-52 antibodies to explore the correlation between antibodies and pharyngeal and laryngeal involvement. (3) Patients were divided into three groups according to serum ferritin levels to investigate the relationship between inflammation and pharyngeal and laryngeal involvement

Statistical analysis

All analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). Data that were consistent with a normal distribution were presented as the mean ± standard deviation, while non-normal distribution data were presented as the median and interquartile range. The independent-sample t-test, Fisher's exact test, or Mann-Whitney test were used

to compare two groups. Multiple comparisons were assessed by Chi-square test. *p*-values <0.05 were considered significant.

Results

Baseline information

Among the 131 anti-MDA5-positive DM patients, the average age was 52.38±12.43 years, and the ratio of males to females was 1:1.67. A total of 35 patients had pharyngeal and laryngeal involvement, with an incidence rate of 26.7%. Among them, 34 patients (97.1%) experienced pharyngalgia, 20 patients (57.1%) had varying degrees of dysphagia, and 22 patients (62.9%) presented with hoarseness. Eleven patients (31.4%) simultaneously experienced dysphagia and hoarseness.

Clinical characteristics of patients with pharyngeal and laryngeal involvement

The 131 anti-MDA5-positive DM patients were divided into two groups based on the presence or absence of pharyngeal and laryngeal involvement. Due to the potential impact of pharyngeal and laryngeal symptoms on food intake, nutrition-related indicators were assessed. The data showed that anti-MDA5-positive DM patients with pharyngeal and laryngeal involvement had significantly lower levels of haemoglobin (104.8±16.3 g/L), albumin (27.9±4.7 g/L), and prealbumin (264.5 [(123,308.8)] mg/L) compared to those without involvement (haemoglobin: 131.6±13.1 g/L, albumin: 38.3±5.3 g/L, prealbumin: 133 [(94,168)] mg/L). Regarding blood lipids, patients with pharyngeal and laryngeal involvement had a high-density lipoprotein level of 0.90±0.27 mmol/L, significantly lower than that of patients without involvement (1.06±0.30 mmol/L, $p<0.01$). However, there were no significant differences in triglyceride, total cholesterol, or low-density lipoprotein levels between the two groups. Patients with pharyngeal and laryngeal involvement showed a high proportion of RP-ILD than that of patients without involvement (27/35, *vs.* 25/96, respectively; $p<0.01$). In terms of prognosis, 13 out of 35 anti-MDA5-positive DM patients with pharyngeal and laryngeal involvement died, while 21 out of 96 patients without involvement died. The difference between the two groups was not statistically significant ($p=0.08$). (Table I).

Table I. Blood test characteristics and prognosis of anti-MDA5-positive DM patients with or without pharyngeal and laryngeal involvement.

	Without pharyngeal and laryngeal involvement (n=96)	With pharyngeal and laryngeal involvement (n=35)	*p*-value
Haemoglobin (g/L)	131.6 ± 13.1	104.8 ± 16.3	<0.01
Albumin (g/L)	38.3 ± 5.3	27.9 ± 4.7	<0.01
Prealbumin (mg/L)	264.5 [(123, 308.8)]	133 [(94,168)]	<0.01
Triglycerides (mmol/L)	1.91 [(1.37, 2.40)]	1.68 [(1.15, 2.07)]	0.08
Total cholesterol (mmol/L)	4.31 ± 1.07	3.97 ± 0.96	0.10
High-density lipoprotein (mmol/L)	1.06 ± 0.30	0.90 ± 0.27	<0.01
Low-density lipoprotein (mmol/L)	2.47 [(1.86, 2.87)]	2.32 [(1.59, 2.62)]	0.06
ILD/RP-ILD (number)	96/25	35/27	<0.01
Death (number)	21	13	0.08

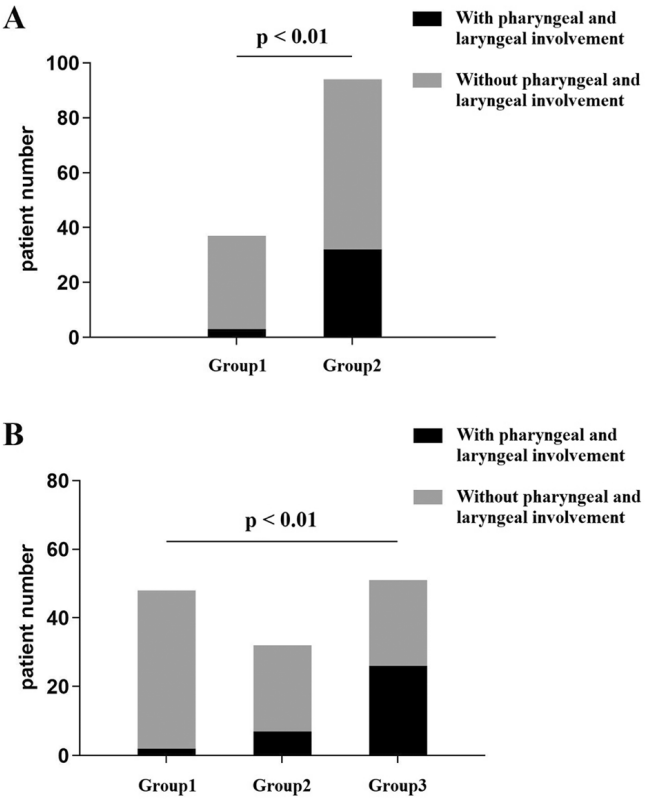

Fig. 1. The clinical characteristics of pharyngeal and laryngeal lesions in patients with anti-MDA5-positive DM.
A: Relationship between pharyngeal and laryngeal involvement and anti-Ro-52 antibodies. In group 1, test for anti-Ro-52 antibodies were negative. (n=37). In group 2, test for anti-Ro-52 antibodies were positive. (n=94).
B: Relationship between pharyngeal and laryngeal involvement and serum ferritin. Group 1: serum ferritin <500 ng/ml (n=48), Group 2: 500 ng/ml ≤ serum ferritin <1000 ng/ml (n=32), and Group 3: 1000 ng/ml ≤ serum ferritin ≤1500 ng/ml (n=51).

Relationship between pharyngeal and laryngeal involvement and anti-Ro-52 antibodies

The 131 anti-MDA5-positive DM patients were divided into two groups based on the presence or absence of anti-Ro-52 antibodies. The results showed that among the 37 patients with negative anti-Ro-52 antibodies, 3 patients (0.08%) had pharyngeal and laryngeal involvement (Group 1). Among the 94 patients with positive anti-Ro-52 antibodies, 32 patients (34.0%) had pharyngeal and laryngeal

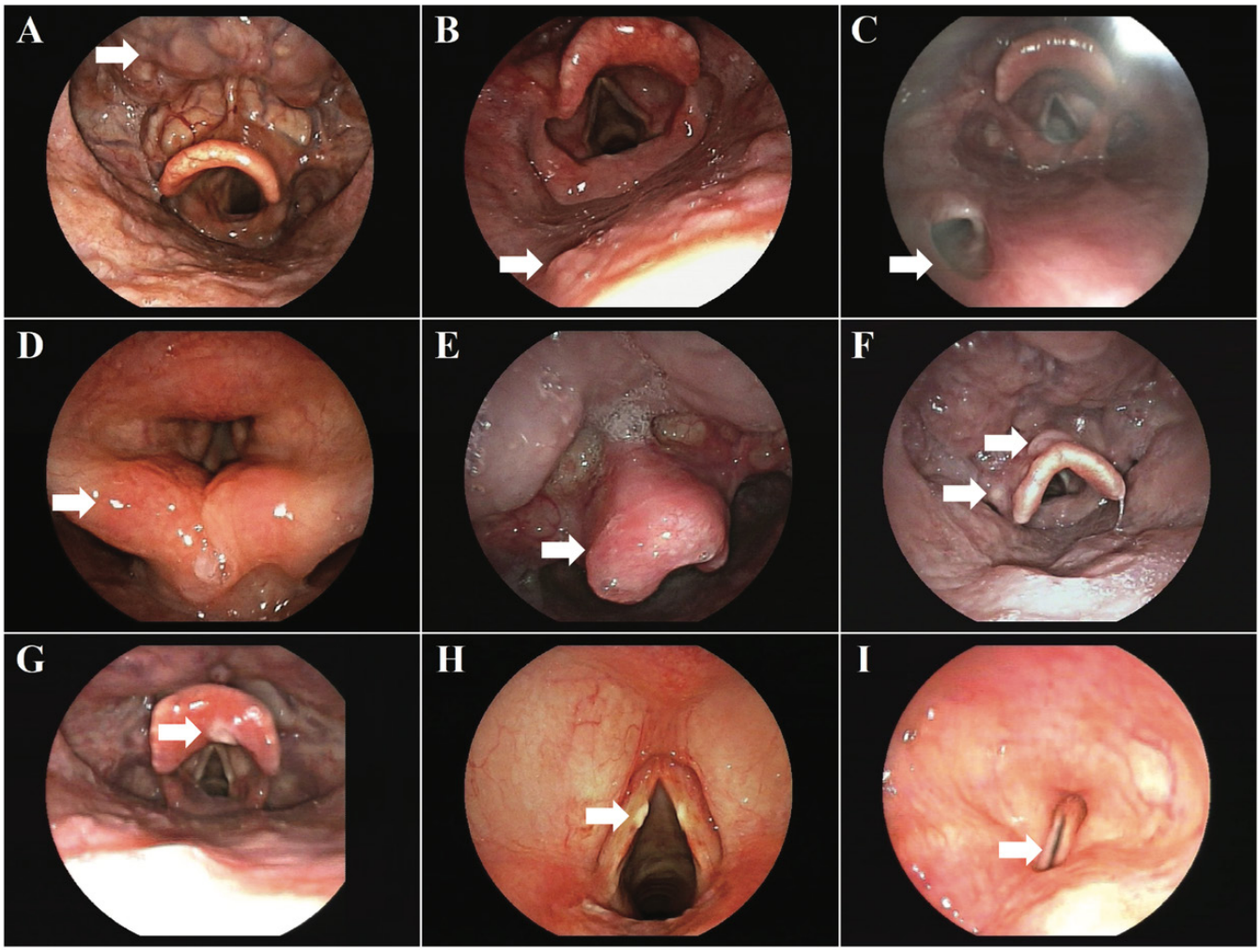

Fig. 2. Characteristics of pharyngeal and laryngeal lesions in anti-MDA5-positive DM patients observed by electronic laryngoscopy.

involvement (Group 2). The difference between the two groups was statistically significant ($p<0.01$). (Fig. 1A).

Relationship between pharyngeal and laryngeal involvement and serum ferritin

The 131 anti-MDA5-positive DM patients were divided into three groups based on serum ferritin levels. In group 1, 48 anti-MDA5-positive DM patients with a low serum ferritin level (serum ferritin <500 ng/ml), only two patients with pharyngeal and laryngeal involvement. 7 patients had pharyngeal and laryngeal involvement in group 2 (500 ng/ml ≤serum ferritin <1000 ng/ml, n=32). Group 3 comprised 51 anti-MDA5-positive DM patients with high level of serum ferritin (1000 ng/ml ≤serum ferritin ≤1500 ng/ml), among these individuals, a total of 10 patients had pharyngeal and laryngeal involvement. The number of anti-MDA5-positive DM patients with pharyngeal and laryngeal involvement in Group 3 was significantly higher than that in Group 1 ($p<0.01$) (Fig. 1B).

Electronic laryngoscopy characteristics of anti-MDA5-positive DM with pharyngeal and laryngeal involvement

All 35 patients with pharyngeal and laryngeal symptoms underwent electronic laryngoscopy examinations. The results showed: (1) Oropharynx: all patients had varying degrees of pharyngeal mucosal hyperaemia. Lingual tonsillar hypertrophy was observed in 33 patients (Fig. 2A, arrow), and posterior pharyngeal wall lymphoid follicle hyperplasia was found in 32 patients (Fig. 2B, arrow). One patient presented with a rare posterior pharyngeal wall fistula formation (Fig. 2C, arrow). Lateral pharyngeal band swelling was observed in 29 patients. (2) Arytenoid area: arytenoid area hyperaemia and swelling were found in 31 patients (Fig. 2D, arrow). (3) Epiglottis: the main manifestations included epiglottic hyperaemia and swelling (Fig. 2E, arrow, n=13), epiglottic hyperplasia (Fig. 2F, arrows, n=6), and epiglottic ulceration (Fig. 2G, arrow, n=1). (4) Vocal cords: Twenty patients had varying degrees of vocal cord hyperaemia. Vocal cord white lesions were observed in 5 patients (Fig. 2H, arrow), and incomplete vocal cord closure was found in 12 patients (Fig. 2I, arrow).

Discussion

Since the discovery of anti-MDA5 antibodies by Japanese scholars, anti-MDA5-positive DM has received increasing clinical attention due to its poor prognosis often associated with

RP-ILD. In addition to this, in clinical practice, we also encounter anti-MDA5-positive DM patients complaining of pharyngeal and laryngeal symptoms. However, related clinical research is relatively scarce. Therefore, we summarised the clinical characteristics of pharyngeal and laryngeal involvement in 131 anti-MDA5-positive DM patients to deepen the understanding of this disease.

Firstly, our single-centre data showed that among 131 anti-MDA5-positive DM patients, the incidence of pharyngeal and laryngeal involvement was as high as 26.7%. Pharyngalgia, dysphagia, and hoarseness were the main clinical symptoms in these patients, suggesting that pharyngeal and laryngeal involvement is a very common complication of anti-MDA5-positive DM, which deserves high attention from rheumatologists.

Secondly, due to symptoms such as pharyngalgia and dysphagia, patients' dietary intake can be greatly affected. Therefore, we further evaluated the nutritional status of the patients. The results indicated that anti-MDA5-positive DM patients with pharyngeal and laryngeal involvement had significantly lower levels of haemoglobin, albumin, prealbumin, and high-density lipoprotein compared to those without involvement. This suggests that pharyngalgia and dysphagia may lead to malnutrition in patients. Conversely, malnutrition may also further aggravate the disease. Current research has confirmed the important relationship between nutrition and immunity. When the body is in a state of malnutrition, the function of immune cells cannot be maintained normally, leading to immunodeficiency. Moreover, malnourished patients themselves are also in a state of chronic systemic inflammation, and elevated serum concentrations of IL-6 can be detected in their bodies (6). However, our prognostic analysis of 131 anti-MDA5-positive DM patients found that the number of deaths among patients with pharyngeal and laryngeal involvement was not significantly higher compared to those without involvement. This indicates that pharyngeal and laryngeal lesions are not decisive factors leading to the death of anti-MDA5-positive DM patients. Currently, it is still believed that uncontrollable interstitial lung disease is more closely related to the death of anti-MDA5-positive DM patients.

Anti-Ro-52 antibodies are currently considered to be an important myositis-associated autoantibody (7). Our previous research showed that anti-MDA5-positive DM patients with positive anti-Ro-52 antibodies are more likely to develop RP-ILD (8) and pulmonary oxidative stress (9). The results of this study showed that the number of patients with pharyngeal and laryngeal involvement was significantly higher in the anti-Ro-52 antibody-positive group compared to the anti-Ro-52 antibody-negative group, further confirming the important role of anti-Ro-52 antibodies in anti-MDA5-positive DM. This also suggests that when anti-MDA5 antibodies and anti-Ro-52 antibodies are simultaneously positive, rheumatologists should evaluate the patient's organ involvement more thoroughly and comprehensively. However, unfortunately, there is still a lack of in-depth research on the mechanism of the relationship between anti-Ro-52 antibodies and dermatomyositis.

High inflammatory status, especially elevated serum ferritin levels, is a significant characteristic of anti-MDA5-positive DM. Takahisa *et al*. (10) even pointed out that anti-MDA5-positive DM may be a type of macrophage activation syndrome mainly in the lungs and serum ferritin is an important indicator to evaluate the response to treatment of RP-ILD in anti-MDA5-positive DM patients. By grouping 131 anti-MDA5-positive DM patients according to different levels of serum ferritin, we found that as inflammatory markers increased, patients were more likely to develop pharyngeal and laryngeal involvement. This is the first study to confirm that the occurrence of pharyngeal and laryngeal symptoms in anti-MDA5-positive DM is closely related to the high inflammatory state of the body.

The above interesting findings prompted us to further perform electronic laryngoscopy examinations on 35 anti-MDA5-positive DM patients with pharyngeal and laryngeal involvement. Electronic laryngoscopy examination is a reliable and commonly used means of detection for the pharyngeal and laryngeal lesions. It can make rapid and definite diagnoses of early inflammation, pharyngeal and laryngeal tumours, vocal cord paralysis, and phonation dysfunction in patients. We found that: i) The main causes of pharyngeal pain in anti-MDA5-positive DM are related to pharyngeal mucosal hyperaemia, lateral pharyngeal band swelling, lingual tonsillar hypertrophy, and posterior pharyngeal wall lymphoid follicle hyperplasia. These manifestations confirm the high inflammatory state of the pharynx in anti-MDA5-positive DM. In addition, we also reported a rare case of posterior pharyngeal wall fistula formation (11). This patient also had severe skin ulcers, suggesting that clinicians should not easily overlook the pharynx and other inconspicuous areas during history taking or physical examination when dealing with dermatomyositis patients with severe skin vasculitis. ii) We also observed varying degrees of hyperaemia and swelling in the arytenoid area of anti-MDA5-positive DM patients. The arytenoid cartilage, on the one hand, cooperates with the epiglottis to participate in swallowing, and on the other hand, it is connected to the vocal cords and regulates their tension. Therefore, inflammatory changes in the arytenoid area can affect patients' swallowing and phonation to a certain extent. iii) We know that the epiglottis is most closely related to swallowing function. The main epiglottic lesions in anti-MDA5-positive DM patients are hyperaemia and swelling. We also observed epiglottic hyperplasia and ulceration in a small number of patients. In autoimmune diseases, epiglottic ulcers are more likely to occur in systemic lupus erythematosus (12) or Behçet's disease (13) patients. This is the first time we have found epiglottic ulcers in anti-MDA5-positive DM patients. This patient also had severe skin rashes (including Gottron's papules, heliotrope rash, V sign, and periungual erythema telangiectasias), but whether there is a correlation between the two requires further research. iv) Vocal cord lesions in anti-MDA5-positive DM patients are

mainly varying degrees of vocal cord hyperaemia and incomplete vocal cord closure, which gives us a more intuitive understanding of patients' hoarseness. Similarly, there are reports of vocal cord palsy in anti-MDA5-positive DM patients, which are considered to be related to severe muscle involvement (14) or prolonged intubation (15). We also found white lesions on the vocal cords in a small number of patients, but unfortunately, we did not perform a biopsy. Scholars have summarized the histopathological examination of vocal cord white lesions in 8 patients with polymyositis and dermatomyositis. The white lesions were mainly fibre necrosis and inflammatory cell infiltration, and good recovery could be achieved through prednisolone, immunosuppressants, and intravenous immunoglobulin therapy (16). Our study and the above research provide us with two very important experiences: a) For anti-MDA5-positive DM patients with pharyngeal and laryngeal symptoms, electronic laryngoscopy should be performed as early as possible to comprehensively evaluate the condition. b) With early diagnosis and targeted treatment, patients' pharyngeal and laryngeal lesions can be effectively recovered.

The limitations of this study must be acknowledged. We only analysed the clinical characteristics of pharyngeal and laryngeal involvement in anti-MDA5-positive DM patients, which may not accurately reflect the characteristics of other types of inflammatory myopathies, such as antisynthetase syndrome. Additionally, electronic laryngoscopy examinations were not performed on patients without pharyngeal and laryngeal symptoms, but the possibility of pharyngeal and laryngeal lesions in this group of patients cannot be excluded. Finally, this work lacks research on the mechanisms of disease occurrence and development, and more fundamental research needs to be carried out in the future.

In conclusion, this study explored the clinical characteristics of anti-MDA5-positive DM with pharyngeal and laryngeal involvement, thereby deepening the understanding of anti-MDA5-positive DM and providing a reliable basis for subsequent research.

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