Clinical Characteristics and Risk Factors for Interstitial Lung Disease in Patients with Idiopathic Inflammatory Myopathy: Postprint

Authors: Li Xingjun, Li Shuangrong, Wang Nan, Wang Xiangyu, Cui Ruomei, Xu Jian, Guo Yulong, Liu Shuang, Liu Shuang

Date: 2023-12-28T00:00:00+00:00

Abstract

Background: Idiopathic inflammatory myopathy (IIM) is a group of connective tissue diseases characterized primarily by muscle inflammation and weakness, with pulmonary involvement being an important factor affecting patient prognosis. Based on myositis-specific autoantibodies (MSAs), IIM can be classified into different clinical subtypes, with variations in clinical manifestations, organ involvement, and prognosis among patients of different subtypes, as well as differing risks of developing interstitial lung disease (ILD).

Objective: To investigate the characteristics of idiopathic inflammatory myopathy and its different clinical subtypes and the risk factors for developing interstitial lung disease.

Methods: Clinical data were collected and organized from patients diagnosed with IIM and hospitalized in the Department of Rheumatology and Immunology, First Affiliated Hospital of Kunming Medical University, between April 2018 and February 2021. Based on myositis-specific autoantibodies, patients were classified into four clinical subtypes: anti-MDA5 antibody-positive dermatomyositis (DM), anti-MDA5 antibody-negative dermatomyositis, immune-mediated necrotizing myopathy (IMNM), and antisynthetase syndrome (ASS). General data, clinical manifestations, and laboratory findings were compared among patients of different subtypes, and a multivariate Logistic regression model was established to explore risk factors for IIM patients developing interstitial lung disease (ILD).

Results: The 150 IIM patients were divided into four clinical subtypes, including 30 cases (20%) of anti-MDA5 antibody-positive DM, 58 cases (38.7%) of anti-MDA5 antibody-negative DM, 14 cases (9.3%) of IMNM, and 48 cases (32.0%) of ASS. The incidence rates of muscle weakness, myalgia, ILD, heliotrope rash,

shawl sign, Gottron's papules/sign, arthralgia, periungual erythema, and dysphagia differed significantly among subtypes (P<0.05). Specifically, the incidence of ILD was higher in both anti-MDA5 antibody-positive DM and ASS subtypes compared to anti-MDA5 antibody-negative DM and IMNM subtypes (P<0.05). The incidence rates of heliotrope rash and shawl sign were higher in both anti-MDA5 antibody-positive and -negative DM subtypes compared to IMNM and ASS subtypes (P<0.05). The incidence of arthralgia was higher in anti-MDA5 antibody-positive DM patients than in anti-MDA5 antibody-negative DM patients (P<0.05). Significant differences were observed among different clinical subtypes in WBC, ALT, AST, serum creatinine, LDH, CK, C4, ferritin, T lymphocytes, CD8+ T lymphocytes, and NK cells (P<0.05). The incidence of ILD differed significantly among IIM patients of different clinical subtypes (P<0.05). Multivariate Logistic regression analysis identified anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, ferritin >403.2 g/L, IgG >14.15 g/L, and LDH >359.5 IU/L as risk factors for IIM-associated ILD.

Conclusion: Clinical manifestations differed significantly among patients of different clinical subtypes, with anti-MDA5 antibody-positive DM patients more likely to present with skin rash, arthralgia, ILD, leukopenia, and other clinical manifestations. Anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, and elevated ferritin, LDH, and IgG are risk factors for IIM-associated ILD.

Full Text

Clinical Characteristics of Patients with Idiopathic Inflammatory Myopathy and Risk Factors for the Development of Interstitial Lung Disease

LI Xingjun[12], **LI Shuangrong**[13], **WANG Nan**[1], **WANG Xiangyu**[1], **CUI Ruomei**[1], **XU Jian**[1], **GUO Yulong**[4], **LIU Shuang**[1]*

[1]Department of Rheumatology and Immunology, First Affiliated Hospital of Kunming Medical University, Kunming 650032, China
[2]Ya'an Polytechnic College, Ya'an 625000, China
[3]Fourth People's Hospital of Zigong City, Zigong 643000, China
[4]Yunnan Fuwai Cardiovascular Hospital, Kunming 650000, China
*Corresponding author: LIU Shuang; E-mail: liushuang_{pku}@163.com

Abstract

Background: Idiopathic inflammatory myopathy (IIM) is a group of connective tissue diseases characterized by muscle inflammation and weakness. Pulmonary involvement represents a critical factor affecting patient prognosis. Based on myositis-specific antibodies (MSAs), IIM can be classified into distinct

clinical subtypes that exhibit significant differences in clinical manifestations, organ involvement, prognosis, and risk of interstitial lung disease (ILD).

Objective: To investigate the clinical characteristics of IIM and its various subtypes, and to identify risk factors for ILD development.

Methods: We retrospectively collected clinical data from patients diagnosed with IIM in the Department of Rheumatology and Immunology at the First Affiliated Hospital of Kunming Medical University between April 2018 and February 2021. Based on MSAs, patients were categorized into four clinical subtypes: anti-MDA5 antibody-positive dermatomyositis (DM), anti-MDA5 antibody-negative DM, immune-mediated necrotizing myositis (IMNM), and anti-synthetase syndrome (ASS). We compared general demographics, clinical manifestations, and laboratory findings across subtypes, and established a multivariate logistic regression model to explore ILD risk factors.

Results: Among 150 IIM patients, 30 (20.0%) had anti-MDA5-positive DM, 58 (38.7%) had anti-MDA5-negative DM, 14 (9.3%) had IMNM, and 48 (32.0%) had ASS. Significant differences existed across subtypes in the incidence of muscle weakness, myalgia, ILD, heliotrope rash, shawl sign, Gottron papules/sign, arthralgia, periungual erythema, and dysphagia ($P<0.05$). ILD occurrence was higher in anti-MDA5-positive DM and ASS subtypes compared to anti-MDA5-negative DM and IMNM subtypes ($P<0.05$). Heliotrope rash and shawl sign were more common in both DM subtypes than in IMNM and ASS ($P<0.05$). Arthralgia incidence was higher in anti-MDA5-positive DM than in anti-MDA5-negative DM ($P<0.05$). Significant inter-subtype differences were also observed in WBC, ALT, AST, serum creatinine, LDH, CK, C4, ferritin, T lymphocytes, CD8+ T cells, and NK cells ($P<0.05$). Multivariate logistic regression analysis identified anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, ferritin >403.2 g/L, IgG >14.15 g/L, and LDH >359.5 IU/L as independent risk factors for ILD in IIM.

Conclusion: Clinical manifestations vary significantly across IIM subtypes. Anti-MDA5-positive DM patients exhibit higher rates of rash, arthralgia, ILD, and leukopenia. Anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, and elevated ferritin, LDH, and IgG levels constitute risk factors for ILD development in IIM.

Keywords: Idiopathic inflammatory myopathy; Clinical subtypes; Myositis-specific antibodies; Interstitial lung disease; Risk factors

Introduction

Idiopathic inflammatory myopathy (IIM) is a heterogeneous group of connective tissue diseases characterized primarily by muscle inflammation and weakness, often accompanied by multi-system and multi-organ involvement. Pulmonary

manifestations include interstitial lung disease (ILD), pleuritis, and pleural effusion, with pulmonary involvement serving as a crucial prognostic factor. Current diagnostic criteria include the 1975 Bohan/Peter criteria and the 2017 EULAR/ACR classification standards. The discovery of myositis-specific antibodies (MSAs) has revolutionized diagnosis, treatment, and prognostic assessment. Based on clinical features and MSAs, researchers have proposed classifying IIM into four clinical subtypes: dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM), and anti-synthetase syndrome (ASS). Additional recognized categories include polymyositis (PM), clinically amyopathic dermatomyositis (CADM), and overlap syndrome. Notably, different MSAs rarely coexist in the same patient, demonstrating mutual exclusivity, and each associates with distinct clinical phenotypes. For instance, anti-melanoma differentiation-associated gene 5 (MDA5) antibodies correlate with severe prognosis and high mortality. This study analyzed 150 IIM patients classified by MSAs into anti-MDA5-positive DM, anti-MDA5-negative DM, IMNM, and ASS subtypes to compare clinical characteristics and identify ILD risk factors, thereby enhancing disease understanding and enabling early assessment and treatment.

Methods

1.1 General Data We retrospectively collected clinical data from patients hospitalized in the Department of Rheumatology and Immunology at the First Affiliated Hospital of Kunming Medical University between April 2018 and February 2021 who met the 2017 EULAR/ACR classification criteria for IIM. Comprehensive clinical information was gathered, including demographics, clinical features, and laboratory findings.

1.2 MSA Measurement All patients underwent serum MSA testing, including anti-SRP, anti-HMGCR, anti-Mi-2, anti-MDA5, anti-NXP2, anti-TIF-1γ, anti-SAE, anti-Ku, anti-NOR-90, anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-ZO, and anti-HA antibodies. With patient consent, serum samples were sent to a third-party laboratory (Jiangsu Simcere Medical Diagnostics) for semi-quantitative determination via immunoblotting. DM-associated antibodies comprised anti-Mi-2, anti-MDA5, anti-NXP2, anti-TIF-1γ, and anti-SAE; IMNM-associated antibodies included anti-SRP and anti-HMGCR; ASS-associated antibodies (anti-synthetase antibodies) included anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-ZO, and anti-HA.

1.3 Study Design Using retrospective analysis, we described baseline characteristics, clinical features, and laboratory results of confirmed IIM patients, comparing differences across subtypes and analyzing ILD risk factors.

1.4 Statistical Analysis All statistical analyses were performed using SPSS 23.0. Continuous variables with normal distribution were expressed as mean $\pm$

standard deviation and compared using ANOVA; non-normally distributed variables were presented as median (P25, P75) and compared using Kruskal-Wallis H test. Categorical data were expressed as percentages and compared using ^{2} test. For ILD risk factor analysis, univariate analysis was first performed. Variables showing significant inter-group differences and those clinically suspected to correlate with ILD were then included in a multivariate logistic regression model. Statistical significance was defined as $P<0.05$.

Results

2.1 General Characteristics The study included 150 IIM patients. Based on MSAs, 30 (20.0%) had anti-MDA5-positive DM, 58 (38.7%) had anti-MDA5-negative DM, 14 (9.3%) had IMNM, and 48 (32.0%) had ASS. No significant differences existed among subtypes in age, sex, age at onset, or disease duration ($P>0.05$) .

2.2 Clinical and Laboratory Comparisons 2.2.1 Clinical Manifestations Significant differences across subtypes were observed in the incidence of muscle weakness, myalgia, ILD, heliotrope rash, shawl sign, Gottron papules/sign, arthralgia, periungual erythema, and dysphagia ($P<0.05$) . ILD rates were higher in anti-MDA5-positive DM and ASS subtypes compared to anti-MDA5-negative DM and IMNM subtypes ($P<0.05$). Both DM subtypes showed higher rates of heliotrope rash and shawl sign than IMNM and ASS ($P<0.05$). Arthralgia was more common in anti-MDA5-positive DM than anti-MDA5-negative DM ($P<0.05$).

2.2.2 Laboratory Indices Significant inter-subtype differences were found in WBC, ALT, AST, serum creatinine, LDH, and CK levels ($P<0.05$) . Pairwise comparisons of these indices across subtypes are presented in [Figure 1: see original paper].

2.2.3 Immunological Parameters Significant differences were observed in C4, ferritin, T lymphocytes, CD8+ T cells, and NK cells across subtypes ($P<0.05$) . Pairwise comparisons of ferritin and CD8+ T cell levels are shown in [Figure 1: see original paper].

2.3 ILD Risk Factor Analysis 2.3.1 Univariate Analysis ILD incidence differed significantly across clinical subtypes ($P<0.05$). Higher ILD rates were associated with pulmonary infection, myalgia, muscle weakness, and arthralgia ($P<0.05$). Disease duration, ALT, AST, LDH, IgG, CRP, CK, and creatinine levels also correlated with ILD occurrence ($P<0.05$) . Literature review suggested associations between ferritin, mechanic's hands, and ILD development ($P<0.1$) .

2.3.2 Multivariate Logistic Regression Analysis Using ILD occurrence as the dependent variable, we performed multivariate logistic regression incorporating statistically significant factors from univariate analysis plus clinically rele-

vant variables (subtype, pulmonary infection, myalgia, muscle weakness, arthralgia, disease duration, CK, ALT, AST, creatinine, LDH, IgG, CRP, ferritin, mechanic's hands, albumin) . The analysis revealed that anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, ferritin >403.2 g/L, IgG >14.15 g/L, and LDH >359.5 IU/L were independent risk factors for ILD in IIM ($P<0.05$) .

Discussion

IIM represents a heterogeneous disease traditionally diagnosed through muscle pain, weakness, and biopsy. However, MSA discovery has enabled early diagnosis in patients presenting with rash, arthralgia, skin ulcers, or ILD. Approximately 70% of IIM patients harbor MSAs, which are mutually exclusive and correlate with specific phenotypes. Anti-Mi-2 antibodies associate with proximal muscle weakness and severe cutaneous manifestations; anti-NXP2 antibodies with subcutaneous calcification; and anti-MDA5 antibodies with digital ulcers and rapidly progressive ILD. ILD prevalence in IIM varies widely (20%-80%). Previous studies reported ILD in approximately 50% of DM patients and nearly all CADM patients, while 86% of anti-Jo-1-positive DM patients had ILD. ASS shows 67%-100% ILD prevalence depending on anti-synthetase antibody subtype, accompanied by rash, arthralgia, mechanic's hands, and Raynaud's phenomenon. IMNM, characterized by markedly elevated muscle enzymes and weakness, rarely involves ILD.

Our study found anti-MDA5-positive DM accounted for 20% of IIM patients, ASS 32%, and IMNM 9.3%, consistent with prior reports. Anti-MDA5-positive DM patients demonstrated higher ILD, rash, and arthralgia rates, with lower WBC and C4 levels and less pronounced enzyme elevation compared to anti-MDA5-negative DM. While some findings align with previous research, discrepancies in ferritin levels and arthralgia rates warrant further investigation with larger cohorts. The lower NK cell count in anti-MDA5-positive DM versus ASS may relate to lymphopenia or immunosuppressive therapy.

IMNM patients exhibited high dysphagia rates and markedly elevated ALT, AST, and CK levels, with low ILD incidence consistent with disease characteristics. However, our small IMNM sample size and lack of muscle biopsy data limit definitive conclusions.

Our study identified anti-MDA5 antibody positivity, anti-synthetase antibody positivity, pulmonary infection, and elevated ferritin, LDH, and IgG as ILD risk factors. These findings align with multiple studies confirming ferritin as a clinical risk factor. While domestic literature has not previously reported IgG and LDH as IIM-ILD risk factors, a study by Zuo et al. identified LDH as a risk factor for rapidly progressive ILD in anti-MDA5-positive DM and ASS, corroborating our results. Serum ferritin >2,200 ng/ml reportedly predicts six-month mortality in anti-MDA5-positive DM with rapidly progressive ILD, reinforcing ferritin's prognostic value.

Limitations and Future Directions

This study's limitations include a relatively small sample size, lack of muscle biopsy data, and absence of ILD subtype classification. Future research should expand sample sizes, incorporate ILD subtyping, and conduct basic studies to identify additional early diagnostic markers to guide clinical practice.

Author Contributions

LI Xingjun: data analysis and manuscript drafting. LI Shuangrong and WANG Nan: data collection. WANG Xiangyu, CUI Ruomei, and XU Jian: manuscript revision. GUO Yulong: statistical analysis and guidance. LIU Shuang: overall manuscript revision and statistical oversight.

Conflict of Interest: None declared.

References

[1] Chinese Medical Association Rheumatology Branch. Guidelines for diagnosis and treatment of polymyositis and dermatomyositis[J]. Chinese Journal of Rheumatology, 2010, 12(14): 828-831. [2] 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[J]. Annals of the Rheumatic Diseases, 2017, 76(12): 1955-1964. [3] MARIAMPILLAI K, GRANGER B, AMELIN D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies[J]. JAMA Neurology, 2018, 75(12): 1528-1534. [4] MAMMEN AL, ALLENBACH Y, STENZEL W, et al. 239th ENMC international workshop: classification of dermatomyositis, Amsterdam, the Netherlands, 14-16 December 2018[J]. Neuromuscular Disorders, 2020, 30(1): 70-92. [5] MCHUGH NJ, TANSLEY SL. Autoantibodies in myositis[J]. Nature Reviews Rheumatology, 2018, 14(5): 290-302. [6] WU W, GUO L, FU Y, et al. Interstitial lung disease in anti-MDA5 positive dermatomyositis[J]. Clinical Reviews in Allergy & Immunology, 2021, 60(2): 293-304. [7] VENCOVSKÝ J, ALEXANDERSON H, LUNDBERG IE. Idiopathic inflammatory myopathies[J]. Rheumatic Diseases Clinics of North America, 2019, 45(4): 569-581. [8] SELVA-O'CALLAGHAN A, PINAL-FERNANDEZ I, TRALLERO-ARAGUáS E, et al. Classification and management of adult inflammatory myopathies[J]. The Lancet Neurology, 2018, 17(9): 816-828. [9] IKEDA S, ARITA M, MISAKI K, et al. Incidence and impact of interstitial lung disease and malignancy in patients with polymyositis, dermatomyositis, and clinically amyopathic dermatomyositis: a retrospective cohort study[J]. SpringerPlus, 2015, 4(240). [10] RICHARDS TJ, EGGER-BEEN A, GIBSON K, et al. Characterization and peripheral blood biomarker assessment of anti-Jo-1 antibody-positive interstitial lung disease[J]. Arthritis and Rheumatism, 2009, 60(7): 2183-2192. [11] HALLOWELL RW, DANOFF SK. Interstitial lung disease associated with the idiopathic inflammatory my-

opathies and the antisynthetase syndrome: recent advances[J]. Current Opinion in Rheumatology, 2014, 26(6): 684-689. [12] WATANABE Y, URUHA A, SUZUKI S, et al. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy[J]. Journal of Neurology, Neurosurgery, and Psychiatry, 2016, 87(10): 1038-1044. [13] LI S, SUN Y, SHAO C, et al. Prognosis of adult idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective study of 679 adult cases[J]. Rheumatology, 2021, 60(3): 1195-1204. [14] TONG Y, ZHANG X, LIANG J. Clinical characteristics of anti-MDA5 antibody associated dermatomyositis complicated with progressive interstitial lung disease[J]. Journal of Fudan University Medical Science, 2021, 1(48): 91-97. [15] FIORENTINO D, CHUNG L, ZWERNER J, et al. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study[J]. Journal of the American Academy of Dermatology, 2011, 65(1): 25-34. [16] LI R, LI XP, LI XM, et al. Prognostic factors of pulmonary interstitial disease associated with inflammatory myopathy[J]. Chinese Journal of Medicine, 2012, 92(33): 2335-2338. [17] LIU L, CHEN Z, TAO JH, et al. Clinical significance of specific antibody profile of idiopathic inflammatory myositis[J]. Chinese Journal of Immunology and Allergy, 2020, 14(2): 135-142. [18] ZUO Y, AN YA, LI C, et al. Analysis of the pathogenesis and immunological characteristics of 146 patients with inflammatory myopathy complicated with pulmonary interstitial disease[J]. Chinese Journal of Rheumatology, 2015, 19(12): 805-812. [19] ZUO Y, YE L, CHEN F, et al. Different multivariable risk factors for rapid progressive interstitial lung disease in anti-MDA5 positive dermatomyositis and anti-synthetase syndrome[J]. Frontiers in Immunology, 2022, 7(13): 845988.

Received: December 7, 2022; Revised: February 28, 2023
Edited by: LI Tingting

Note: Figure translations are in progress. See original paper for figures.