Clinical Rheumatology (2024) 43:1381–1392
https://doi.org/10.1007/s10067-024-06899-3

ORIGINAL ARTICLE

Prognostic factors of fungal infection in anti-melanoma differentiation-associated gene 5 antibody-positive associated interstitial lung disease

Wanqing Zhou[1] · Haoran Chen[1] · Tong Ji[2] · Ranxun Chen[2] · Qingqing Xu[1,2] · Lulu Chen[1,2] · Min Cao[1,2] · Hourong Cai[1,2] · Jinghong Dai[1,2]

Received: 29 August 2023 / Revised: 31 December 2023 / Accepted: 1 February 2024 / Published online: 12 February 2024

Abstract

Objective To investigate the potential risk factors for mortality in fungal infection in anti-melanoma differentiation-associated gene 5 antibody-positive associated interstitial lung disease (MDA5-ILD).

Methods Patients diagnosed with MDA5-ILD from April 2017 to November 2022 were included. The demographic data, laboratory examinations, therapeutic and follow-up information were recorded. Fungal infection diagnosis was established based on a combinations of host factors, clinical features and mycologic evidences. High-dose corticosteroid therapy was defined as the initial corticosteroid doses > 240mg/d. The primary endpoint was mortality. Potential factors for fungal infection occurrence and prognostic factors were analyzed using logistic regression analysis and Cox proportional hazards regression.

Results In total, 121 patients with MDA5-ILD were included. During follow-up, 41 (33.9%) patients had suffered fungal infection and 39.0% (16/41) of whom had ever received high-dose corticosteroid therapy. The median interval from corticosteroid use to the occurrence of fungal infection was 29 (10–48) days. The mean survival time of patients with fungal infection was 234.32 ± 464.76 days. The mortality in MDA5-ILD with fungal infection was 85.4% (35/41), which was significantly higher than those without (85.4% VS 56.3%, $P < 0.001$). High-dose corticosteroid therapy ($P = 0.049$) was independent risk factor for fungal infection occurrence. Decreased serum albumin level ($P = 0.024$) and high-dose corticosteroid therapy ($P = 0.008$) were both associated with increased mortality in MDA5-ILD patients with fungal infection.

Conclusion Fungal infection is associated with an increased mortality in MDA5-ILD. The serum albumin level and corticosteroid dose should be taken into consideration when treating MDA5-ILD.

Key Points

- *This study showed fungal infection is associated with an increased mortality in MDA5-ILD. In MDA5-ILD patients with fungal infection, the presence of decreased serum albumin level and high-dose corticosteroid therapy were identified as predictors for mortality.*

Keywords Anti-MDA5 · Fungal infection · Idiopathic inflammatory myopathies · Interstitial lung disease

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of systemic autoimmune disorders which affect multiple organs, including skin, muscle, and lung [1]. Among them, interstitial lung disease (ILD) is the leading extramuscular manifestation of IIMs, which significantly contributes to an increased morbidity and mortality [2–4]. Accumulating evidence suggests that myositis specific autoantibodies (MSAs) represent clinically useful biomarkers that help identify the distinct subtypes of IIMs [2]. Notably, anti-melanoma differentiation-associated

✉ Jinghong Dai
daijinghong@nju.edu.cn

[1] Department of Pulmonary and Critical Care Medicine, Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University, No. 321 Zhongshan Road, Nanjing 210008, Jiangsu, China

[2] Department of Pulmonary and Critical Care Medicine, Nanjing Drum Tower Hospital, The Afliated Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China

gene 5 (MDA5) antibody is strongly associated with amyopathic dermatomyositis which was characterized as minimal or no muscle involvement with hallmark cutaneous lesions of dermatomyositis and an increased susceptibility to develop rapidly progressive ILD (RP-ILD) [4–6]. Despite the early detection and aggressive therapy, the short-term mortality in MDA5-ILD remains as high as 50% [7, 8].

High doses corticosteroids and calcineurin antagonists in combination with cyclophosphamide have been recommended in MDA5-ILD [8, 9]. Other treatment including rituximab, plasmapheresis, veno-venous extracorporeal membrane oxygenation, and lung transplantation et al. have been reported [10]. High-dose corticosteroids, multiply immunosuppressants and lymphopenia were also risk factors for infection in IIMs [11, 12]. Recently, there has been an increase in the incidence of fungal infections, which have been associated with poor prognosis [13–15]. Timely detection and management of fungal infection may improve long-term outcomes. However, few studies have investigated the risk and prognostic factors of fungal infection in patients with MDA5-ILD. In this study, we aimed to assess the incidence of fungal infection among patients with MDA5-ILD. Additionally, we explore the risk factors and prognostic indicators for fungal infection in individuals with MDA5-ILD.

Methods

Subjects studied and inclusion criteria

A total of 470 IIMs-ILD patients were retrospectively analyzed in Nanjing Drum Tower Hospital from April 2017 to November 2022. The diagnosis of IIMs was based on the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) IIM classification criteria or the 2018 EMNC DM criteria [16, 17]. All patients underwent detection of MSAs, including anti-Mi-2, anti-TIF1-y, anti-MDA5, anti-NXP2, anti-SRP, and anti-ARS antibodies (anti-Jo-1, anti-PL-7, anti-PL -12, anti-EJ, and anti-OJ). Among the 470 patients, 121 (25.7%) had anti-MDA5 antibodies, 241 (51.3%) had anti-ARS antibodies, 14 (3.0%) had anti-SRP antibodies, 3 (0.6%) had anti-Mi-2 antibodies, 2 (0.4%) had anti-TIF1-y antibodies, 1 (0.2%) had anti-NXP2 antibodies, and 51 (10.9%) were MSA negative. ILD diagnosis was established based on clinical symptoms, physical examinations, and hallmark abnormalities present in chest high-resolution computed tomography (HRCT), after excluding other identifiable causes such as drug-induced, environmental exposure and secondary to other known connective tissue diseases, etc. [18]. RP-ILD was diagnosed when the following conditions were met within the past 4 weeks: a rapidly deterioration of respiratory symptoms leading to severe hypoxic respiratory failure with arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300mmHg; newly-emerging abnormalities on chest HRCT including the ground-glass opacities or consolidations or the reticulation or honeycombing with the exclusion of identified causes, such as acute heart failure or pulmonary atrial embolism, etc. [19].

Diagnostic criteria for fungal infection

This study focuses on fungal pneumonias and oral candidiasis infection. The diagnosis of fungal pneumonias was based on the latest consensus definitions from the European Organization for Research and Treatment of Cancer (EORTC), the Mycoses Study Group Education and Research Consortium (MSGERC), and the International Society for Heart and Lung Transplantation (ISHLT) [20]. Patients who fulfilled at least 1 host factors, 1 clinical features and 1 mycologic evidence were considered probable fungal pneumonias cases [20]:

Host factors:

(1) Neutropenia occurred recently (neutrophil count < 500 /μ l for > 10 days).
(2) Hematologic malignancy.
(3) Receipt of allogeneic hematopoietic stem cell transplantation or solid organ transplantation.
(4) Corticosteroids have been used for more than 3 weeks within the previous 60 days (above 0.3mg/kg/d, except for allergic bronchopulmonary aspergillosis).
(5) Application of T cell immunosuppressant or B cell immunosuppressant within 90 days.
(6) The patient also has AIDS or hereditary immunodeficiency (such as chronic granuloma or combined immunodeficiency disease).
(7) Acute graft-versus-host disease, grade III or IV, involving the intestines, lungs or liver, with poor response to steroids therapy.

Clinical features:

The presence of 1 of the following 4 patterns on CT:

(1) Dense, well-defined lesions with or without halo sign.
(2) Air crescent sign.
(3) Cavity.
(4) Wedge-shaped, segmental or lobar lesions.

Mycologic evidence:

(1) Any mold recovered by culture from sputum, BAL, bronchial brush, or aspirate.
(2) Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold.
(3) Galactomannan test (GM test) antigen positive in plasma, serum, bronchoalveolar lavage fluid or cerebrospinal fluid.

(4) Two consecutive sera (1p3)-Bmuri D-glucan test (G test) were positive.

Oral candidiasis infection was diagnosed based on clinical symptoms/signs and laboratory tests such as smear fungal test and/or saliva's fungal culture [21]. Pyogenic infection was defined as the presence of bacteria in sputum culture or blood culture or an increase in bacterial count in urine routine.

Clinical data

Clinical information was obtained by retrospectively reviewing patients' records at the time of the patients' first admission to the hospital, including demographic data, laboratory examinations, and therapeutic information. Laboratory examinations we collected included the following: oxygenation index (PaO_2/FiO_2), red blood cell count (RBC), white blood cell count (WBC), neutrophil percentage, lymphocytes percentage, CD4 + lymphocytes count, hemoglobin, platelets, albumin, creatine kinase (CK), lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) etc. Therapeutic information comprised the high-dose corticosteroid therapy, initial intravenous corticosteroid dose, oral corticosteroid daily dose, the corticosteroid tapering duration, immunosuppressive agents used, intravenous immune globulin (IVIG), and the utilization of antifungal medications. High-dose corticosteroid therapy was defined as the doses of corticosteroid on day 1 or 2 at start of treatment > 240mg/d [22]. The oral corticosteroid daily dose at was defined as the dose at discharge, and corticosteroid tapering duration was the time from initial treatment to the oral corticosteroid daily dose or infection.

Follow-up data

The vital status was determined through medical record reviews and telephone communications. Survival time was measured as the interval from the first HRCT indicating the diagnosis of ILD to death. Clinical outcomes including 3-month and overall mortality were recorded. Follow-up data were collected until March 2023.

Statistical analysis

Qualitative data were presented as numbers and percentage, and quantitative data as mean and standard deviation (SD) or median and interquartile range (IQR). Continuous variables were analyzed using a two-tailed Student's t-test or the Mann−Whitney U test while categorical variables were assessed using the chi-square test or Fisher's exact test when necessary. Survival probability was evaluated utilizing the Kaplan–Meier model and survival curves were compared via the log-rank test. Univariate and multivariate logistic regression analysis were conducted to identify potential factors associated with fungal infection occurrence. Prognostic factors were determined using Cox proportional hazards regression analysis. Variables that exhibited significance in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using SPSS 25.0 software (SPSS, Chicago, Illinois). A two-sided p-value of ≤ 0.05 was regarded statistically significant.

Results

Demographic and clinical characteristics of MDA5-ILD patients with or without fungal infection

In total, 121 patients diagnosed with MDA5-ILD were included. They were 74 (61.2%) females and 47 (38.8%) males, whose mean age was 56.49 ± 10.14 years (range: 31–86 years). Of these patients, 24 (19.8%) had a history of smoking, and the mean duration from symptom onset to diagnosis was 4.68 ± 9.03 months. 41 (33.9%) patients were diagnosed as fungal infection. Overall, 26 (21.5%) patients developed pyogenic infection. Among the 26 patients with pyogenic infection, 14 (53.8) were combined with fungal infection. Overall, 32.2% (39/121) of patients developed RP-ILD. 43.6% (17/39) of RP-ILD patients occurred fungal infection when 29.3% (24/82) of non-RP-ILD patients occurred fungal infection. The median interval from corticosteroid use to the occurrence of fungal infection was 29 (10–48) days (Fig. 1). 85.4% (35/41) of fungal infection were diagnosed within 3 months following the use of corticosteroid.

The constitution of anti-MDA5 antibody titers differed between the two groups, with more strong positive patients (23/41, 56.1%) in patients with fungal infection than in patients without (25/80, 31.3%, $p = 0.030$). The number of patients with weak, moderate, and strong positive anti-MDA5 antibody titers in patients with fungal infection were 9, 9, and 23, and in patients without were 29, 26 and 25, respectively. Comparing patients with fungal infection to those without it revealed that respiratory failure occurred more frequently among those with fungal infection (78.0% VS 55.0%, $P = 0.013$, Table 1), while the mean duration from symptom onset to diagnosis was significantly shorter in this group of patients (2.67 ± 3.11 VS 5.71 ± 10.77 months, $P = 0.021$, Table 1). No statistically significant difference was found regarding sex, age, and underlying disease between patients with and without fungal infections. As summarised in Table 1, patients with fungal infection had significantly lower PaO2/FiO2 levels ($P = 0.006$), lymphocyte percentage ($P = 0.010$), albumin levels ($P = 0.002$), and CD4 + lymphocyte counts

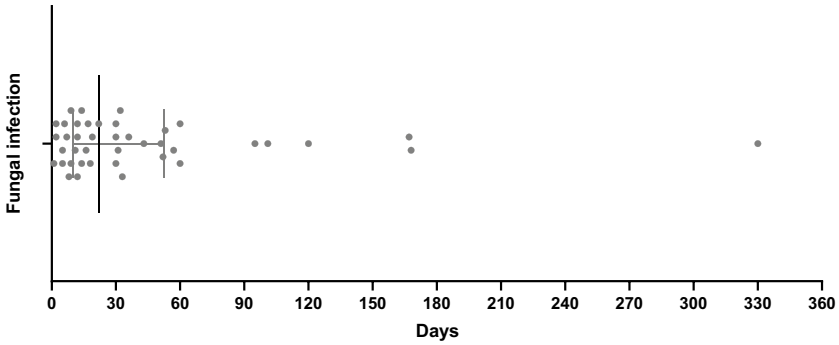

Fig. 1 The median interval from corticosteroid use to fungal infection

($P=0.005$) than those without fungal infection, while the values of neutrophil percentage ($P=0.004$), LDH ($P=0.042$), ferritin ($P=0.008$) and ESR ($P=0.017$) were significantly higher in patients with fungal infection.

The level of β-DG was increased in 24 patients with fungal infection. Among them, the level of β-DG in 10 patients decreased after anti-fungal treatment, in 2 patients still increased progressively, and 12 patients were not reexamined after treatment. 61 patients (50.4%) had reexamined CD4 + lymphocyte counts at intervals ranging from 7–14 days after corticosteroid therapy. The mean level of CD4 + lymphocyte counts change was 124.59 ± 299.50 10^6/L. The change rate of CD4 + lymphocyte counts had no significant differences in patients with or without fungal infection.

Among the 41 patients, 63.4% (26/41) had fungal pneumonias, 26.8% (11/41) had oral candidiasis infection and 9.8% (4/41) had both fungal pneumonias and oral candidiasis infection. We classified these 4 patients as fungal pneumonias group. In patients with fungal pneumonias, 36.7% (11/30) were infected with angioinvasive molds and 63.3% (19/30) were infected with invasive candida. Candida was the main fungal infection. There was no significant difference in clinical characteristics, laboratory examinations, therapeutic information information and mortality between the two groups (Table 2).

Therapeutic information of MDA5-ILD patients with fungal infection

Among the 121 patients, 81 (66.9%) had received antibiotics prior to admission, 65 (53.7%) had received irregular corticosteroid or immunosuppressive therapy, and 18 (14.9%) had not received any medications. The first presentation was ILD in 105 (86.8%) patients, and rash or muscle symptoms in 16 (13.2%) patients.

All patients were initially treated with intravenous corticosteroid at a mean dosage of 230.09 ± 177.46 mg on day 1 or 2. Among them, 11 (11/121, 9.1%) patients were treated with corticosteroid monotherapy, 50 (50/121, 41.3%) patients were treated with corticosteroid and one immunosuppressant agent, whereas 60 (60/121, 49.6%) patients were treated with corticosteroid combined with two or more immunosuppressants, including cyclophosphamide in 57 (57/121, 47.1%) patients, tacrolimus in 53 (53/121, 43.8%) patients, tofacitinib in 29 (29/121, 24.0%) patients, cyclosporine A in 16 (16/121, 13.2%) patients, hydroxychloroquine in 13 (13/121, 10.7%) patients, and other immunosuppressants (including tripterygium wilfordii, azathioprine, and mycophenolate) in 5 (5/121, 4.1%) patients.

80 (80/121, 66.1%) patients were not infected with fungal. The mean corticosteroid tapering duration was 537.34 ± 647.67 days. The mean initial intravenous corticosteroid dose was 188.95 ± 145.34 mg, and the mean oral corticosteroid daily dose was 35.91 ± 7.64 mg/day.

41 (41/121, 33.9%) patients were infected with fungal. 31.7% (13/41) were treated with corticosteroid and one immunosuppressant agent, while 51.2% (21/41) were treated with corticosteroid combined with two or more immunosuppressants; only 17.1% (7/41) of patients were treated with corticosteroid monotherapy alone. The specific therapeutic regimen is presented in Table 3. Notably, the combination of cyclophosphamide and tacrolimus was the most commonly therapeutic regimen (24.4%). The mean corticosteroid tapering duration was 227.17 ± 444.50 days. The mean initial intravenous corticosteroid dose was 310.26 ± 206.88 mg, and the mean oral corticosteroid daily dose was 36.56 ± 5.98 mg/day. In comparison to patients without fungal infection, those with fungal infection more frequently received high-dose corticosteroid therapy (39.0% vs 15.0%, $P=0.003$, Table 1). The corticosteroid tapering duration was significantly shorter in patients with fungal infection than those without ($p=0.003$). Additionally, IVIG was more frequently applied in patients with fungal infection than in those without (58.5% vs 20.0%, $P<0.001$, Table 1). The oral corticosteroid daily dose between patients with or without fungal infection showed no significant difference ($P=0.754$). 73.2% (30/41) patients were treated with antifungal agents. The most common antifungal agent was fluconazole (17/30, 56.7%), followed by caspofungin (9/30, 30.0%), and voriconazole (6/30, 20.0%). Furthermore, 70.7% (29/41) patients received sulfamethoxazole (SMZ) treatment.

Table 1 Clinical characteristics in patients with MDA5-ILD, with or without fungal infection

	All patients ($n=121$)	With fungal infection ($n=41$)	Without fungal infection ($n=80$)	*P*-value
Age at diagnosis, yrs	56.49 ± 10.14	58.17 ± 9.07	55.63 ± 10.60	0.192
Male	47 (38.8%)	12 (29.3%)	35 (43.8%)	0.122
Smoking	24 (19.8%)	9 (22.0%)	15 (18.8%)	0.676
Duration from symptoms onset to diagnosis, months	4.68 ± 9.03	2.67 ± 3.11	5.71 ± 10.77	0.021
RP-ILD	39 (32.2%)	17 (41.5%)	22 (27.5%)	0.120
Respiratory failure	76 (62.8%)	32 (78.0%)	44 (55.0%)	0.013
Malignancy	5 (4.1%)	1 (2.4%)	4 (5.0%)	0.661
Hypertension	23 (19.0%)	9 (22.0%)	14 (17.5%)	0.555
Diabetes mellitus	20 (16.5%)	8 (19.5%)	12 (15.0%)	0.527
Pyogenic infection	26 (21.5%)	14 (34.1%)	12 (15.0%)	0.015
Anti-SSA antibodies	10 (8.3%)	5 (12.2%)	5 (6.3%)	0.304
Anti-MDA5 antibody level				0.030
Weak positive (+)	38 (31.4%)	9 (22.0%)	29 (36.3%)	
Moderate positive (++)	35 (28.9%)	9 (22.0%)	26 (32.5%)	
Strong positive (+++)	48 (39.7%)	23 (56.1%)	25 (31.3%)	
Laboratory examinations				
PaO2/FiO2	256.05 ± 105.42	219.14 ± 95.63	276.05 ± 105.69	0.006
RBC, 10^9/L	4.17 ± 0.67	4.07 ± 0.59	4.22 ± 0.70	0.256
WBC, 10^9/L	6.76 ± 2.97	7.32 ± 3.57	6.48 ± 2.58	0.140
Neutropenia	5 (4.1%)	3 (7.3%)	2 (2.5%)	0.335
Neutrophil percentage, %	78.67 ± 12.26	83.13 ± 9.80	76.39 ± 12.81	0.004
Lymphocytes percentage, %	14.34 ± 9.24	11.34 ± 7.55	15.88 ± 9.68	0.010
Hemoglobin, g/L	122.59 ± 19.46	120.07 ± 18.13	123.88 ± 20.10	0.311
Platelets, 10^9/L	205.21 ± 72.66	189.71 ± 62.98	213.16 ± 76.30	0.093
Albumin, g/L	33.13 ± 4.00	31.61 ± 3.43	33.92 ± 4.07	0.002
CK, U/L	70.83 ± 70.72	73.31 ± 77.63	69.41 ± 67.00	0.785
LDH, U/L	452.98 ± 372.60	568.66 ± 507.04	392.18 ± 261.40	0.042
CRP, mg/dl	21.14 ± 28.66	26.70 ± 29.30	18.18 ± 28.05	0.124
Ferritin, ng/ml	1062.44 ± 601.19	1309.52 ± 471.72	902.56 ± 627.49	0.008
ESR, mm/h	41.28 ± 23.09	48.31 ± 23.32	37.42 ± 22.18	0.017
CD4 lymphocytes count, 10^6/L	333.77 ± 276.18	250.63 ± 171.96	376.41 ± 309.01	0.005
CD4 lymphocytes count change, 10^6/L	124.59 ± 299.50	52.32 ± 297.48	165.36 ± 296.64	0.159
Initial treatment				
Initial intravenous corticosteroid dose, mg	230.09 ± 177.46	310.26 ± 206.88	188.95 ± 145.34	0.002
Oral corticosteroid daily dose, mg/day	36.06 ± 7.27	36.56 ± 5.98	35.91 ± 7.64	0.754
Corticosteroid tapering duration, days	432.24 ± 603.12	227.17 ± 444.50	537.34 ± 647.67	0.003
High-dose corticosteroid therapy	28 (23.1%)	16 (39.0%)	12 (15.0%)	0.003
Total number of immunosuppressant				0.056
0	11 (9.1%)	7 (17.1%)	4 (5.0%)	
1	50 (41.3%)	13 (31.7%)	37 (46.3%)	
> = 2	60 (49.6%)	21 (51.2%)	39 (48.8%)	
IVIG	40 (33.1%)	24 (58.5%)	16 (20.0%)	< 0.001
SMZ	73 (60.3%)	29 (70.7%)	44 (55.0%)	0.094
Mortality	66.1% (80/121)	85.4% (35/41)	56.3% (45/80)	< 0.001
Mortality within 3 months	52.1% (63/121)	85.7% (30/35)	38.4% (33/86)	< 0.001
Mortality above 3 months	29.3% (17/58)	45.5% (5/11)	25.5% (12/47)	0.239

Data are mean ± SD or number (%). Continuous variables were compared using a two-tailed Student's t test. Categorical variables were compared using the chi-square test, or Fisher's exact test when needed. *RP-ILD* Rapidly progressive interstitial lung disease; *PaO2/FiO2* Oxygenation index; RBC: red blood cell; *WBC* White blood cell; *CK* Creatine kinase; *LDH* Lactate dehydrogenase; *CRP* C-reactive protein; *ESR* Erythrocyte sedimentation rate; *IVIG* Intravenous immune globulin; *SMZ* Sulfamethoxazole

Table 2 Clinical characteristics in patients with fungal pneumonias or with oral candidiasis infection

	With fungal infection ($n=41$)	Fungal pneumonias ($n=30$)	Oral candidiasis infection ($n=11$)	*P*-value
Age at diagnosis, yrs	58.17 ± 9.07	56.87 ± 9.07	61.73 ± 8.46	0.130
Male	12 (29.3%)	9 (30.0%)	3 (27.3%)	> 0.999
Smoking	9 (22.0%)	7 (23.3%)	2 (18.2%)	> 0.999
Duration from symptoms onset to diagnosis, months	2.67 ± 3.11	2.38 ± 2.71	3.47 ± 4.06	0.326
RP-ILD	17 (41.5%)	14 (46.7%)	3 (27.3%)	0.309
Respiratory failure	32 (78.0%)	24 (80.0%)	8 (72.7%)	0.680
Malignancy	1 (2.4%)	1 (3.3%)	0 (0.0%)	> 0.999
Hypertension	9 (22.0%)	8 (26.7%)	1 (9.1%)	0.401
Diabetes mellitus	8 (19.5%)	6 (20.0%)	2 (18.2%)	> 0.999
Anti-SSA antibodies	5 (12.2%)	3 (10.0%)	2 (18.2%)	0.598
Anti-MDA5 antibody level				0.373
Weak positive (+)	9 (22.0%)	7 (23.3%)	2 (18.2%)	
Moderate positive (++)	9 (22.0%)	8 (26.7%)	1 (9.1%)	
Strong positive (+++)	23 (56.1%)	15 (50.0%)	8 (72.7%)	
Laboratory examinations				
PaO2/FiO2	219.14 ± 95.63	214.00 ± 93.06	234.03 ± 106.48	0.575
RBC, 10^9/L	4.07 ± 0.59	4.07 ± 0.56	4.08 ± 0.70	0.959
WBC, 10^9/L	6.76 ± 2.97	7.74 ± 3.75	6.16 ± 2.88	0.215
Neutrophil percentage, %	83.13 ± 9.80	84.00 ± 9.15	80.76 ± 11.53	0.355
Lymphocytes percentage, %	11.34 ± 7.55	10.59 ± 7.07	13.40 ± 8.77	0.296
Hemoglobin, g/L	120.07 ± 18.13	120.50 ± 17.61	118.91 ± 20.32	0.807
Platelets, 10^9/L	189.71 ± 62.98	186.73 ± 62.72	197.82 ± 66.03	0.624
Albumin, g/L	31.61 ± 3.43	31.78 ± 3.49	31.15 ± 3.40	0.605
CK, U/L	73.31 ± 77.63	80.93 ± 87.40	51.20 ± 30.81	0.302
LDH, U/L	568.66 ± 507.04	614.40 ± 582.14	443.91 ± 148.89	0.347
CRP, mg/dl	26.70 ± 29.30	32.08 ± 32.30	12.02 ± 9.13	0.004
Ferritin, ng/ml	1309.52 ± 471.72	1330.06 ± 455.85	1217.08 ± 605.13	0.676
ESR, mm/h	48.31 ± 23.32	51.57 ± 23.98	40.00 ± 20.19	0.166
CD4 lymphocytes count, 10^6/L	250.63 ± 171.96	267.38 ± 182.60	206.45 ± 137.85	0.323
Initial treatment				
Initial intravenous corticosteroid dose, mg	310.26 ± 206.88	342.76 ± 213.79	216.00 ± 158.83	0.095
Oral corticosteroid daily dose, mg/day	36.56 ± 5.98	36.00 ± 6.99	37.50 ± 4.18	0.643
Corticosteroid tapering duration, days	227.17 ± 444.50	201.73 ± 467.47	296.55 ± 386.46	0.552
High-dose corticosteroid therapy	16 (39.0%)	14 (46.7%)	2 (18.2%)	0.096
Total number of immunosuppressant				0.633
0	7 (17.1%)	6 (20.0%)	1 (9.1%)	
1	13 (31.7%)	8 (26.7%)	5 (45.5%)	
> = 2	21 (51.2%)	16 (53.3%)	5 (45.5%)	
IVIG	24 (58.5%)	19 (63.3%)	5 (45.5%)	0.476
SMZ	29 (70.7%)	22 (73.3%)	7 (63.6%)	0.405
Mortality	85.4% (35/41)	90.0% (27/30)	72.7% (8/11)	0.316

Data are mean ± SD or number (%). Continuous variables were compared using a two-tailed Student's t test. Categorical variables were compared using the chi-square test, or Fisher's exact test when needed. *RP-ILD* Rapidly progressive interstitial lung disease; *PaO2/FiO2* Oxygenation index; *RBC* Red blood cell; *WBC* White blood cell; *CK* Creatine kinase; *LDH* Lactate dehydrogenase; *CRP* C-reactive protein; *ESR* Erythrocyte sedimentation rate; *IVIG* Intravenous immune globulin; *SMZ* Sulfamethoxazole

Table 3 Therapeutic information of MDA5-ILD patients with fungal infection

	Patients with fungal infection ($n=41$)
Type of infection	
Fungal pneumonias	30 (73.2%)
Oral candidiasis infection	11 (26.8%)
Median interval from corticosteroid use to fungal infection (day)	29 (10–48)
Infection within 3 months	35 (85.4%)
Corticosteroid	
Initial intravenous corticosteroid dose, mg	310.26 ± 206.88
High-dose corticosteroid therapy	16 (39.0%)
Total number of immunosuppressant	
0	7 (17.1%)
1	13 (31.7%)
> =2	21 (51.2%)
Immunosuppressant progaram	
CsA	3 (7.3%)
CY	3 (7.3%)
Tac	4 (9.8%)
Tofacitinib	2 (4.9%)
HCQ	1 (2.4%)
CY + CsA	1 (2.4%)
CY + Tac	10 (24.4%)
CY + tofacitinib	3 (7.3%)
HCQ + Tac	2 (4.9%)
Others	5 (12.2%)
IVIG	24 (58.5%)
Antifungal medications	30 (73.2%)
Fluconazole	17 (46.4%)
Voriconazole	6 (14.6%)
Caspofungin	9 (22.0%)
SMZ	29 (70.7%)

Data are mean ± SD or number (%). *CsA* Cyclosporine A; *Tac* Tacrolimus; *CY* Cyclophosphamide; *HCQ* Hydroxychloroquine; *IVIG* Intravenous immune globulin; *SMZ* Sulfamethoxazole

Risk factors of fungal infection in patients with MDA5 + IIMs-ILD

To elucidate potential risk factors for fungal infection, a univariate analysis was carried out using the logistic regression model (Table 4). Respiratory failure ($P=0.015$), decreased CD4 + lymphocytes count ($P=0.026$), and high-dose corticosteroid therapy ($P=0.004$) were significantly associated with fungal infection in patients with MDA5-ILD during univariate analysis. Following adjustment for confounding variables through multivariate analysis, independent risk factors for fungal infection was identified as high-dose corticosteroid therapy ($P=0.049$) (Table 4).

Mortality and prognostic factors of MDA5-ILD patients with fungal infection

The mean follow-up time for this cohort was 442.19 ± 623.49 days (range 1–3030 days). The mortality rate for the entire MDA5-ILD cohort was 66.1% (80/121, Table 1). Among the 80 nonsurvivors, 31.3% (25/80) experienced fungal infection, 8.8% (7/80) experienced pyogenic infection, 12.5% (10/80) experienced both fungal infection and pyogenic infection, and 47.5% (38/80) experienced no infection (Table 5). The main cause of mortality (42.5%, 34/80) was respiratory failure related acute exacerbation of ILD. 32.5% (26/80) of patients died of severe infection, and the cause of mortality of 25% (20/80) of patients was unknown. In MDA5-ILD patients, those with fungal infections had a significantly higher mortality rate compared to those without (85.4% vs 56.3%, $P<0.001$, Fig. 2A). However, there was no significant difference in mortality rate between the fungal pneumonias group and the oral candidiasis infection group (90.0% vs 72.7%, $P=0.272$, Fig. 2B). Interestingly, the majority of fungal infection occurred within the first 3 months after the use of corticosteroid (35/41, 85.4%), which coincided with the highest patient mortality rate during that period (30/35, 85.7%). The mean time from corticosteroid use to fungal infection was 43.41 ± 53.55 days. The 3-month mortality rate for patients with fungal infection was also higher than patients without (85.7% vs 38.4%, $P<0.001$, Fig. 2C) while the mortality rate above 3 months showed no difference between patients with or without fungal infection (45.5% vs 25.5%, $P=0.239$, Fig. 2D).

To identify poor prognostic factors in MDA5-ILD patients with fungal infection, we conducted a multivariate Cox regression analysis (Table 6). Univariate analysis indicated that seven factors were closely linked to poor outcomes in this patient cohort: respiratory failure ($P=0.017$), increased WBC ($P=0.024$), decreased lymphocytes percentage ($P=0.038$), decreased serum albumin level ($P=0.035$), increased serum LDH level ($P=0.017$), increased serum CRP level ($P=0.028$), and received high-dose corticosteroid therapy ($P=0.050$). After adjusting for confounding factors, multivariate analysis showed that decreased serum albumin level ($P=0.024$), and high-dose corticosteroid therapy ($P=0.008$) were independent risk factors for poor prognosis in MDA5-ILD patients with fungal infection.

Discussion

This retrospective study showed that the incidence of fungal infection in MDA5-ILD was 33.9% (41/121). The median interval from corticosteroid use to fungal infection was 29 (10–48) days. Patients with fungal infection were found to have a reduced survival compared to those without (85.4% VS 56.3%, $P<0.001$). Clinicians should

Table 4 Multivariate logistic regression analysis of risk factors for fungal infection in patients with MDA5-ILD

Variable	Univariate analysis			Multivariate analysis		
	OR	*P*-value	95%CI	OR	*P*-value	95%CI
Age, yrs	1.026	0.192	0.987–1.065			
Male	0.532	0.124	0.238–1.190			
Smoking	1.219	0.676	0.482–3.084			
RP-ILD	1.867	0.122	0.846–4.122			
Respiratory failure	2.909	0.015	1.230–6.880	1.513	0.415	0.559–4.093
Malignancy	0.475	0.512	0.051–4.393			
Hypertension	1.326	0.555	0.519–3.387			
Diabetes mellitus	1.374	0.528	0.512–3.684			
Neutropenia	3.079	0.229	0.494–19.208			
CD4 lymphocytes count, 10^6/L	0.998	0.026	0.996–1.000	0.998	0.151	0.996–1.001
High-dose corticosteroid therapy	3.627	0.004	1.508–8.723	2.605	0.049	1.003–6.768

RP-ILD Rapidly progressive interstitial lung disease

be alerted to the possible presence of fungal infection in patients who have received high-dose corticosteroid therapy. Adjusted Cox proportional hazards model identified that decreased serum albumin level and high-dose corticosteroid therapy were both associated with the mortality.

Infection was one of the most common complications in patients with IIMs. Recent studies indicated that infections occured in approximately 30% of IIMs patients during hospitalization, including septicemia, pneumonia/ empyema, digestive tract infection, etc. [23, 24]. In a retrospective study involving 279 polymyositis/dermatomyositis (PM/DM) patients, 104 (37%) severe infections occurred in PM/DM patients. Among them, 68% were pyogenic, and 36% were opportunistic infection (fungal, viral, and mycobacterial) [23]. Yong Peng Ge et al. indicated that the incidence of infection was 27.6% in IIM patients and methylprednisolone pulse (OR = 3.22, $P = 0.001$) was independent risk factors for infection [12]. The incidence of fungal infection in rheumatic diseases depending on the study design and populations. For instance, invasive fungal infection has been found to occur in 16.7% of patients with systemic lupus erythematosus (SLE) [25]. A singal center study in China also showed that 17.0% (142/834) of patients with rheumatic diseases progressed to cytomegalovirus pneumonia [26]. An observational study showed that 1.5% (3/204) of patients with IIMs dignosied with fungal infection, accounting for 16.7% of all opportunistic infections [11]. In another study involving 160 juvenile myositis patients, the incidence of pneumocystis jirovecii pneumonia (PJP) was 8.1% [27]. Few studies have focused on fungal infections in patients with ILD associated with IIMs. MDA5-ILD patients with fungal infection base in a large single-center sample have been identified for the first time. Our study found that 33.9% (41/121) of patients experienced fungal infection. This high morbidity rate may be attributed to anti-MDA5 antibodies, as they have been identified as a risk factor for developing infection [13, 28]. This may be attributed that patients with anti-MDA5 positive often have pulmonary interstitial fibrosis, broken lung defense barriers, decreased CD4 + T cell counts, and aggressive immunosuppressive therapy, which increases the risk of infection [13, 28].

Table 5 Clinical characteristics of nonsurvivors with MDA5-ILD

	Nonsurvivors ($n = 80$)
Type of infection	
Fungal infection	25 (31.3%)
Pyogenic infection	7 (8.8%)
Both fungal infection and pyogenic infection	10 (12.5%)
No infection	38 (47.5%)
Cause of mortality	
Respiratory failure	34 (42.5%)
Severe infection	26 (32.5%)
Unknown	20 (25.0%)
Died within 3 months	63 (78.8%)
Died above 3 months	17 (21.2%)

Data are number (%). Unknown: Some patients were confirmed dead by telephone communications, but the specific cause of death was not clear

The mortality rate is high in patients with fungal infections. Previous studies have shown that PJP + group more frequently exhibited RP-ILD and fever in MDA5-DM patients [13]. The mortality was 4 times more frequent in patients with invasive fungal infection than in SLE patients without the deep fungal infection [25]. Jun Li et al. also indicated that the PJP + patients had a significantly greater risk of mortality compared with the PJP − patients (69.2% vs. 13.0% $P < 0.001$) [14]. In another study, opportunistic fungal infection was independently associated with hospital mortality among DM patients; 3% of DM nonsurvivors carried a diagnosis of opportunistic fungal infection [15].

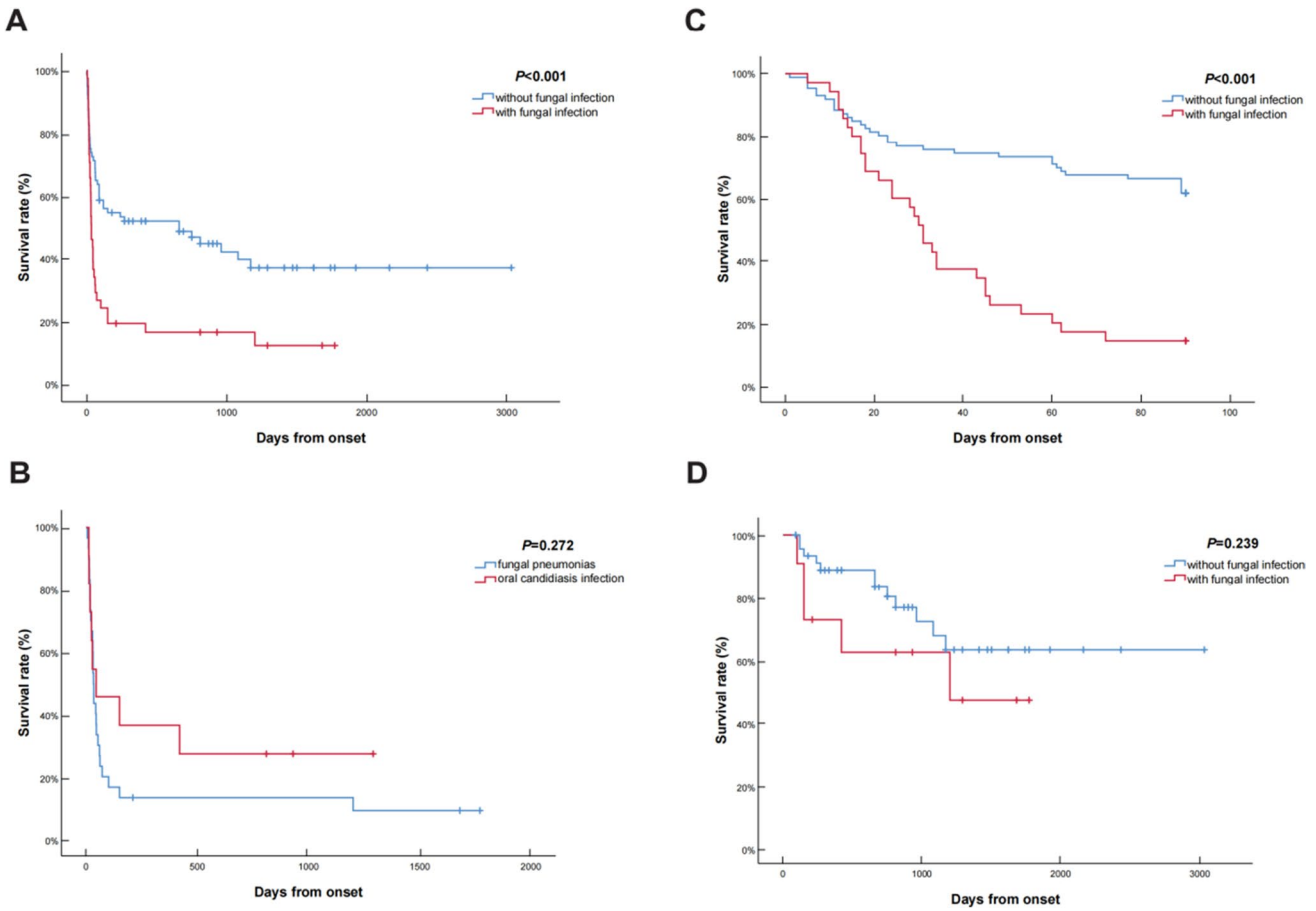

Fig. 2 Survival curves for MDA5-ILD patients. **A** Survival curves for MDA5-ILD patients with or without fungal infection. **B** Survival curves for MDA5-ILD patients with fungal pneumonias or with oral candidiasis infection. **C** Survival curves for MDA5-ILD patients with or without fungal infection within 3 months. **D** Survival curves for MDA5-ILD patients with or without fungal infection above 3 months

Our study indicates that the mortality rate is higher among patients with fungal infection compared to those without. Older age, increased LDH and decreased CD4 + T cell counts were reported as risk factors for mortality in rheumatic diseases combined with opportunistic infection [13, 26, 29, 30]. Peripheral blood lymphopenia was in association with corticosteroids for its ability to impair lymphocyte proliferation, inhibit T cell function and block the production of inflammatory cytokines [31, 32]. Our study revealed that decreased serum albumin level and high-dose corticosteroid therapy were independently associated with mortality in fungal infection patients. Many previous studies have indicated that decreased serum albumin was associated with increased mortality in several disease including autoimmune disorder, pediatric adenovirus pneumonia, and coronavirus disease 2019 [33–35]. This may be explained by that serum albumin is the main serum protein involved in drug binding and transport, so it may affect the efficacy of some antifungal drugs, thus further affecting mortality [33]. Another possible cause is severe hypoproteinemia caused by a cytokine storm caused by infection, which is related to the intensification of disease-related inflammation and the progression of the disease, which eventually leads to the death of the patient [35]. Current studies still recommend high-dose corticosteroids as the first choice for MDA5-DM patients. Future prospective studies were needed to explore the specific effect of corticosteroids on mortality in patients with opportunistic infection.

Jun Won Park et al. recommend that trimethoprim/sulfamethoxazole (TMP-SMX) prophylaxis (given as one double-strength tablet three times a week or as one single-strength tablet per day, started on the first day of high-dose steroid treatment and was stopped when the daily steroid dose was tapered) as an effective therapy for the prevention of PJP infection in patients with rheumatic disease receiving prolonged, high-dose steroids [36]. Therefore, timely prevention and identification of fungal infection is crucial for the treatment of MDA5-ILD. The majority of fungal infection occurred during the first 3 months of disease progression; this period also showed the highest mortality rate. Many previous studies on PJP have also indicated that PJP

Table 6 Multivariate cox regression analysis of prognostic factors in MDA5-ILD patients with fungal infection

Variable	Univariate analysis			Multivariate analysis		
	HR	*P*-value	95%CI	HR	*P*-value	95%CI
Age, yrs	1.021	0.298	0.981–1.063			
Male	1.173	0.663	0.571–2.411			
Smoking	0.921	0.845	0.401–2.111			
RP-ILD	1.829	0.081	0.928–3.604			
Respiratory failure	2.953	0.017	1.211–7.200			
Malignancy	3.504	0.232	0.448–27.388			
Hypertension	0.953	0.906	0.428–2.119			
Diabetes mellitus	0.607	0.268	0.251–1.469			
Anti-SSA antibodies	0.190	0.452	0.138–1.482			
WBC, 10^9/L	1.132	0.024	1.016–1.261			
Neutrophil percentage, %	1.038	0.065	0.998–1.080			
Lymphocytes percentage, %	0.943	0.038	0.892–0.997			
Albumin, g/L	0.901	0.035	0.818–0.993	0.873	0.024	0.776–0.982
CK, U/L	1.000	0.995	0.996–1.005			
LDH, U/L	1.001	0.017	1.000–1.001	1.001	0.052	1.000–1.002
CRP, mg/dl	1.011	0.028	1.001–1.022	1.002	0.727	0.990–1.015
ESR, mm/h	1.002	0.818	0.988–1.016			
CD4 lymphocytes count, 10^6/L	0.118	0.068	0.012–1.168			
High-dose corticosteroid therapy	2.030	0.050	1.001–4.118	2.861	0.008	1.308–6.258
Total number of Immunosuppressant ≤1 vs ≥2	0.563	0.094	0.287–1.102			
Antifungal medications	1.032	0.936	0.483–2.205			
SMZ	1.777	0.141	0.827–3.816			

RP-ILD Rapidly progressive interstitial lung disease; *WBC* White blood cell; *CK* Creatine kinase; *LDH* Lactate dehydrogenase; *CRP* C-reactive protein; *ESR* Erythrocyte sedimentation rate; *SMZ* Sulfamethoxazole

often occurred approximately 3 months after the MDA5-IIMs diagnosis [13, 14, 25]. This finding can be explained by the following two facts: (1) Patients with MDA5-IIMs received potent induction immunosuppressive therapy as the initial therapy, which could increase the risk of fungal infection [14]. (2) Anti-MDA5 + patients have a systemic syndrome with three subgroups with different prognosis, which distinct from other IIMs patients. The patients with acute onset and rapid deterioration of respiratory failure within 3 months had a high early mortality and a poor prognosis. Patients with a course of disease more than 3 months tend to have a better prognosis [37]. This suggests that clinicians should focus on preventing early infection and mortality in MDA5-ILD patients.

This current study had several limitations. Firstly, it was conducted retrospectively in a single-center, making selection bias inevitable. Additionally, the sample size of our cohort was relatively small, which could have affected the generalizability of the results. Secondly, due to the retrospective nature of the study, there were some variations in the use of corticosteroid treatment options among patients. Therefore, strict unification of treatment options was difficult to achieve, which may have influenced the outcome measures.

Conclusion

In conclusion, Fungal infection is common in MDA5-ILD patients and is associated with more severe illness and poorer outcomes. Our results demonstrated that high-dose corticosteroid therapy independently predicted a higher risk of fungal infection occurrence. In MDA5-ILD patients with fungal infection, the presence of decreased serum albumin level and high-dose corticosteroid therapy were identified as predictors for mortality. These findings carry clinical significance, emphasizing the importance of optimizing treatment strategies in MDA5-ILD to prevent fungal infections. Further long-term studies are needed to investigate the prophylactic measures that can be taken to prevent fungal infections in IIMs-ILD patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-024-06899-3.

Funding The study was supported by the National Natural Science Foundation of China (81570058, 82170076).

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations This was a retrospective study and the ethical approval was acquired in accordance with the policy of the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University.

Disclosures None.

References

1. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, Milisenda JC, Grau-Junyent JM, Mammen AL (2018) Classification and management of adult inflammatory myopathies. Lancet Neurol 17(9):816–828. https://doi.org/10.1016/S1474-4422(18)30254-0
2. Labirua A, Lundberg IE (2010) Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. Curr Opin Rheumatol 22(6):633–638. https://doi.org/10.1097/BOR.0b013e32833f1970
3. Lilleker JB, Vencovsky J, Wang G, Wedderburn LR, Diederichsen LP, Schmidt J, Oakley P, Benveniste O, Danieli MG, Danko K, Thuy NTP, Vazquez-Del Mercado M, Andersson H, De Paepe B, deBleecker JL, Maurer B, McCann LJ, Pipitone N, McHugh N, Betteridge ZE, …, all EuroMyositis contributors (2018) The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis 77(1):30–39. https://doi.org/10.1136/annrheumdis-2017-211868
4. Li Y, Gao X, Li Y, Jia X, Zhang X, Xu Y, Gan Y, Li S, Chen R, He J, Sun X (2020) Predictors and mortality of rapidly progressive interstitial lung disease in patients with idiopathic inflammatory myopathy: a series of 474 patients. Front Med 7:363. https://doi.org/10.3389/fmed.2020.00363
5. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EK (2017) A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. Clin Rev Allergy Immunol 52(1):1–19. https://doi.org/10.1007/s12016-015-8510-y
6. Mammen AL (2011) Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. Nat Rev Neurol 7(6):343–354. https://doi.org/10.1038/nrneurol.2011.63
7. Tsuji H, Nakashima R, Hosono Y, Imura Y, Yagita M, Yoshifuji H, Hirata S, Nojima T, Sugiyama E, Hatta K, Taguchi Y, Katayama M, Tanizawa K, Handa T, Uozumi R, Akizuki S, Murakami K, Hashimoto M, Tanaka M, Ohmura K, …, Mimori T (2020) Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. Arthritis Rheumatol (Hoboken, N.J.) 72(3):488–498. https://doi.org/10.1002/art.41105
8. Romero-Bueno F, Diaz Del Campo P, Trallero-Araguás E, Ruiz-Rodríguez JC, Castellvi I, Rodriguez-Nieto MJ, Martínez-Becerra MJ, Sanchez-Pernaute O, Pinal-Fernandez I, Solanich X, Gono T, Gonzalez-Gay MA, Plana MN, Selva-O'Callaghan A, MEDRA5 (Spanish MDA5 Register) group (listed contributors at the end of the article) (2020) Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin Arthritis Rheum 50(4):776–790. https://doi.org/10.1016/j.semarthrit.2020.03.007
9. Bay P, de Chambrun MP, Rothstein V, Mahevas M, De Prost N, Roux A, Zuber B, Biet DI, Hervier B, Tazi A, Mouthon L, Mekinian A, Deligny C, Borie R, Meurice JC, Meyer A, Priou P, Savale L, De Saint Martin L, Gallay L, …, Uzunhan Y (2022) Efficacy of plasma exchange in patients with anti-MDA5 rapidly progressive interstitial lung disease. J Autoimmun 133:102941. https://doi.org/10.1016/j.jaut.2022.102941
10. Kurasawa K, Arai S, Namiki Y, Tanaka A, Takamura Y, Owada T, Arima M, Maezawa R (2018) Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. Rheumatology (Oxford) 57(12):2114–2119. https://doi.org/10.1093/rheumatology/key188
11. Redondo-Benito A, Curran A, Villar-Gomez A, Trallero-Araguas E, Fernández-Codina A, Pinal-Fernandez I, Rodrigo-Pendás JÁ, Selva-O'Callaghan A (2018) Opportunistic infections in patients with idiopathic inflammatory myopathies. Int J Rheum Dis 21(2):487–496. https://doi.org/10.1111/1756-185X.13255
12. Ge YP, Shu XM, He LR, Wang GC, Lu X (2022) Infection is not rare in patients with idiopathic inflammatory myopathies. Clin Exp Rheumatol 40(2):254–259. https://doi.org/10.55563/clinexprheumatol/yps7ai
13. Chen X, Shu X, He L, Yang H, Lu X, Wang G, Ge Y (2023) High prevalence and mortality of Pneumocystis jirovecii pneumonia in anti-MDA5 antibody-positive dermatomyositis. Rheumatology (Oxford, England):kead063. https://doi.org/10.1093/rheumatology/kead063. (Advance online publication)
14. Li J, Wang S, Zheng J, Li Q, Li J, Lu L (2023) Clinical characteristics of and risk factors for pneumocystis jirovecii pneumonia in anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive dermatomyositis patients: a single-center retrospective study. Clin Rheumatol 42(2):453–462. https://doi.org/10.1007/s10067-022-06403-9
15. Murray SG, Schmajuk G, Trupin L, Lawson E, Cascino M, Barton J, Margaretten M, Katz PP, Yelin EH, Yazdany J (2015) A population-based study of infection-related hospital mortality in patients with dermatomyositis/polymyositis. Arthritis Care Res 67(5):673–680. https://doi.org/10.1002/acr.22501
16. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Dankó K, Dimachkie MM, Feldman BM, Torre IG, Gordon P, …, International Myositis Classification Criteria Project consortium, The Euromyositis register and The Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland) (2017) 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis 76(12):1955–1964. https://doi.org/10.1136/annrheumdis-2017-211468
17. Mammen AL, Allenbach Y, Stenzel W, Benveniste O, ENMC 239th Workshop Study Group (2020) 239th ENMC International Workshop: classification of dermatomyositis, Amsterdam, the Netherlands, 14–16 December 2018. Neuromuscul Dis 30(1):70–92. https://doi.org/10.1016/j.nmd.2019.10.005
18. Travis W. D., Costabel, U., Hansell, D. M., King, T. E., Jr, Lynch, D. A., Nicholson, A. G., Ryerson, C. J., Ryu, J. H., Selman, M., Wells, A. U., Behr, J., Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, …, ATS/ERS Committee on Idiopathic Interstitial Pneumonias (2013) 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 188(6):733–748. https://doi.org/10.1164/rccm.201308-1483ST
19. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, Sun L (2013) Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. Arthritis Care Res 65(8):1316–1324. https://doi.org/10.1002/acr.21985
20. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, …, Pappas PG (2020) Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis 71(6):1367–1376. https://doi.org/10.1093/cid/ciz1008
21. Hu L, Mao Q, Zhou P, Lv X, Hua H, Yan Z (2019) Effects of streptococcus salivarius K12 with nystatin on oral candidiasis-RCT. Oral Dis 25(6):1573–1580. https://doi.org/10.1111/odi.13142
22. Kiser TH, Allen RR, Valuck RJ, Moss M, Vandivier RW (2014) Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 189(9):1052–1064. https://doi.org/10.1164/rccm.201401-0058OC
23. Marie I, Ménard JF, Hachulla E, Chérin P, Benveniste O, Tiev K, Hatron PY (2011) Infectious complications in polymyositis and dermatomyositis: a series of 279 patients. Semin Arthritis Rheum 41(1):48–60. https://doi.org/10.1016/j.semarthrit.2010.08.003
24. Chen IJ, Tsai WP, Wu YJ, Luo SF, Ho HH, Liou LB, Chen JY, Kuo CF, Chang HC, Yang CH, Yu KH (2010) Infections in polymyositis and dermatomyositis: analysis of 192 cases. Rheumatology (Oxford) 49(12):2429–2437. https://doi.org/10.1093/rheumatology/keq279
25. Martínez-Martínez MU, Herrera-Van Oostdam D, Román-Acosta S, Magaña-Aquino M, Baranda-Cándido L, Abud-Mendoza C (2012) Invasive fungal infections in patients with systemic lupus erythematosus. J Rheumatol 39(9):1814–1818. https://doi.org/10.3899/jrheum.111498
26. Xue Y, Jiang L, Wan WG, Chen YM, Zhang J, Zhang ZC (2016) Cytomegalovirus pneumonia in patients with rheumatic diseases after immunosuppressive therapy: a single center study in China. Chin Med J 129(3):267–273. https://doi.org/10.4103/0366-6999.174490
27. Sabbagh SE, Neely J, Chow A, DeGuzman M, Lai J, Lvovich S, McGrath T, Pereira M, Pinal-Fernandez I, Roberts J, Rouster-Stevens K, Schmeling H, Sura A, Tarshish G, Tucker L, Rider LG, Kim S, CARRA JDM Workgroup and the Childhood Myositis Heterogeneity Study Group (2021) Risk factors associated with Pneumocystis jirovecii pneumonia in juvenile myositis in North America. Rheumatology (Oxford) 60(2):829–836. https://doi.org/10.1093/rheumatology/keaa436
28. Cheng L, Li Y, Wu Y, Luo Y, Zhou Y, Liao Z, Wen J, Liang X, Wu T, Tan C, Liu Y (2023) Risk of early infection in idiopathic inflammatory myopathies: cluster analysis based on clinical features and biomarkers. Inflammation 46(3):1036–1046. https://doi.org/10.1007/s10753-023-01790-w
29. Huang L, Fu Q, Ye Y, Lin Y, Yan Q, Chen S (2021) High incidence and mortality of pneumocystis jirovecii infection in anti-MDA5-antibody-positive dermatomyositis: experience from a single center. Arthritis Res Ther 23(1):232. https://doi.org/10.1186/s13075-021-02606-8
30. Takizawa Y, Inokuma S, Tanaka Y, Saito K, Atsumi T, Hirakata M, Kameda H, Hirohata S, Kondo H, Kumagai S, Tanaka Y (2008) Clinical characteristics of cytomegalovirus infection in rheumatic diseases: multicentre survey in a large patient population. Rheumatology (Oxford) 47(9):1373–1378. https://doi.org/10.1093/rheumatology/ken231
31. Connors M, Kovacs JA, Krevat S, Gea-Banacloche JC, Sneller MC, Flanigan M, Metcalf JA, Walker RE, Falloon J, Baseler M, Feuerstein I, Masur H, Lane HC (1997) HIV infection induces changes in CD4+ T-cell phenotype and depletions within the CD4+ T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. Nat Med 3(5):533–540. https://doi.org/10.1038/nm0597-533
32. Weekes MP, Wills MR, Sissons JG, Carmichael AJ (2004) Long-term stable expanded human CD4+ T cell clones specific for human cytomegalovirus are distributed in both CD45RAhigh and CD45ROhigh populations. J Immunol (Baltimore, Md.: 1950) 173(9):5843–5851. https://doi.org/10.4049/jimmunol.173.9.5843
33. Ward ES, Gelinas D, Dreesen E, Van Santbergen J, Andersen JT, Silvestri NJ, Kiss JE, Sleep D, Rader DJ, Kastelein JJP, Louagie E, Vidarsson G, Spriet I (2022) Clinical significance of serum albumin and implications of FcRn inhibitor treatment in IgG-mediated autoimmune disorders. Front Immunol 13:892534. https://doi.org/10.3389/fimmu.2022.892534
34. Zhang J, Zhu Y, Zhou Y, Gao F, Qiu X, Li J, Yuan H, Jin W, Lin W (2023) Pediatric adenovirus pneumonia: clinical practice and current treatment. Front Med 10:1207568. https://doi.org/10.3389/fmed.2023.1207568
35. Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, Ni L, Zhang XA, Wang DW (2020) Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. Sci China Life Sci 63(11):1678–1687. https://doi.org/10.1007/s11427-020-1733-4
36. Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB (2018) Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis 77(5):644–649. https://doi.org/10.1136/annrheumdis-2017-211796
37. Allenbach Y, Uzunhan Y, Toquet S, Leroux G, Gallay L, Marquet A, Meyer A, Guillaud C, Limal N, Gagnadoux F, Hervier B, Borie R, Deligny C, Terrier B, Berezne A, Audia S, Champtiaux N, Devilliers H, Voermans N, Diot E, …, French Myositis Network (2020) Different phenotypes in dermatomyositis associated with anti-MDA5 antibody: study of 121 cases. Neurology 95(1):e70–e78. https://doi.org/10.1212/WNL.0000000000009727