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ORIGINAL RESEARCH

Clinical, radiological and pathological features of anti-MDA5 antibody-associated interstitial lung disease

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ABSTRACT

Introduction To investigate the clinical, radiographic and pathological features of interstitial lung disease (ILD) in patients with anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis (anti-MDA5+DM).

Methods We retrospectively analysed the medical records of patients with anti-MDA5+DM who had undergone radiological examination, and lung histopathology was performed on 17 of them.

Results This study examined 329 patients with anti-MDA5+DM, of whom 308 (93.6%) were diagnosed with ILD and 177 (53.8%) exhibited rapidly progressive ILD (RPILD). The most common radiographic patterns were organising pneumonia (OP) (43.2%), non-specific interstitial pneumonia (NSIP) (26.4%) and NSIP+OP (18.5%). Histological analysis showed NSIP (41.2%) and NSIP+OP (47.1%) to be the predominant patterns. However, in the 17 patients who underwent lung histopathology, the coincidence rate between radiological and histopathological diagnoses was only 11.8%. Compared with patients without RPILD, those with RPILD showed a higher prevalence of NSIP+OP (26.6% vs 10.7%, p=0.001) and a lower prevalence of NSIP pattern (21.5% vs 37.4%, p=0.002) on high-resolution CT. Furthermore, patients with radiographic patterns of NSIP+OP or diffuse alveolar damage (DAD) had more risk factors for poor prognosis, with 12-month mortality rates of 45.9% and 100%, respectively.

Conclusions RPILD was commonly observed in patients with anti-MDA5+DM. OP was identified as the predominant radiographic pattern, which corresponded to a histopathological pattern of NSIP or NSIP+OP. Notably, patients exhibiting radiographic patterns of NSIP+OP or DAD were shown to have a poor prognosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interstitial lung disease (ILD) is a serious and frequently fatal complication observed in patients with anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis (anti-MDA5+DM); however, the full clinical, radiological and pathological characteristics remain unclear.

WHAT THIS STUDY ADDS

⇒ This large cohort study demonstrated that organising pneumonia (OP) was the predominant radiological pattern in anti-MDA5+DM ILD, with a corresponding pathological pattern of non-specific interstitial pneumonia (NSIP) or NSIP+OP.

⇒ Radiographic NSIP+OP may serve as an early clinical predictor of rapidly progressive ILD and poor prognosis.

⇒ Mortality rates were significantly higher among patients presenting with radiographic patterns of diffuse alveolar damage and NSIP+OP, highlighting the importance of early detection and management of these conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Familiarity with the unique clinical, radiological and pathological features of anti-MDA5+DM ILD may help elucidate its underlying pathophysiological mechanisms and disease behaviour in the future.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a rare group of autoimmune diseases with a heterogeneous yet highly specific spectrum of muscular and systemic involvement.[1] The clinical manifestations, treatment responses and prognoses are variable, and myositis-specific antibodies (MSAs) appear to be associated with distinct clinical phenotypes. Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a distinct MSA identified in 2005.[2] The clinical presentation of anti-MDA5 antibody-positive dermatomyositis (anti-MDA5+DM) differs substantially from the other subtypes of IIM, with characteristic interstitial lung disease (ILD) and skin-articular symptoms.[3 4]

The prognosis of anti-MDA5+DM is relatively poor due to a high prevalence of rapidly progressive interstitial lung disease (RPILD).[5] In the East Asian population, ILD occurs in

82%–100% of patients with anti-MDA5+DM and RPILD occurs in 39%–100% of patients, which are obviously higher than that of the Caucasian populations.[6] ILD can be divided into several subtypes, such as non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), usual interstitial pneumonia (UIP) and diffuse alveolar damage (DAD).[7] Previous studies have suggested that different ILD patterns in patients with IIM are associated with different prognoses.[8] However, large-scale clinical studies exploring the exact radiological and pathological features of anti-MDA5+DM-associated ILD (anti-MDA5+DM ILD) are still lacking, with only a few case reports and small-sample studies.[9–11] Accordingly, we aimed to clarify the clinical characteristics, radiological features and pathological features of anti-MDA5+DM ILD in a relatively large cohort and to identify the disease progression profile of different patterns of ILD.

METHODS

Patient selection

Patients diagnosed with anti-MDA5+DM were retrospectively analysed at the Rheumatology Department of the China-Japan Friendship Hospital from January 2016 to March 2022. Anti-MDA5+DM diagnosis was established based on the Bohan and Peter criteria,[12] and retrospectively reconfirmed according to the 2017 EULAR/American College of Rheumatology IIM classification criteria[13] or the 2018 ENMC DM criteria[14] by two experienced rheumatologists. Patients with anti-MDA5+DM with available chest high-resolution CT (HRCT) scans were enrolled for clinical and radiological analyses.

The MSA profile that included the anti-MDA5 antibody was identified by immunoblotting according to the manufacturer's instruction (EUROIMMUN, Lübeck, Germany). For this retrospective study, patient consent was not required because patient privacy was maintained and patient care was not affected.

Clinical data

Patients' demographic data, laboratory test results and follow-up information were recorded in detail. Laboratory test results included lymphocyte count and levels of creatine kinase, lactate dehydrogenase (LDH), ferritin and anti-Ro-52 antibody. The criteria used to define infection were based on definitive aetiological evidence from laboratory test results according to previous literature.[15] We defined disease onset as the date when the patient first reported symptoms, while disease duration was measured as the time between disease onset and the date of the first hospitalisation. For the purpose of defining RPILD in anti-MDA5+DM, the study used terminology based on guidelines from the American Thoracic Society for progressive disease in idiopathic pulmonary fibrosis.[16] Specifically, RPILD was defined as either worsening dyspnoea and chest HRCT progression within 1 month or deterioration to respiratory failure within 3 months since onset of respiratory symptoms. Patients who did not meet these criteria were classified as having non-RPILD.

Radiological analysis

All participants underwent HRCT in a supine position at the end of inspiration from the lung apex to the lung base on a multilayer spiral CT device (Lightspeed VCT/64, GE Healthcare, Milwaukee, Wisconsin, USA; Toshiba Aquilion One TSX-301C/320, Toshiba, Tokyo, Japan; Philips iCT/256, Philips Healthcare, Best, The Netherlands; or Siemens FLASH Dual Source CT, Siemens Healthcare, Forchheim, Germany). The HRCT scanning protocol was of spiral mode with the following acquisition and reconstruction parameters: tube voltage of 100–120 kV, tube current of 100–300 mAs, section thickness of 0.625–1 mm, table speed of 39.37 mm/s, gantry rotation time of 0.8 s and reconstruction increment of 1–1.25 mm.

All HRCT images for the diagnosis of ILD were independently reviewed by two experienced radiologists without any prior knowledge of this study. Disagreements between the two radiologists were resolved by consensus. The following HRCT findings were noted: ground-glass opacity (GGO), consolidation, reticulation, traction bronchiectasis, honeycombing, lower lung volume loss, emphysema, cyst, swollen mediastinal lymph nodes, pleural irregularities and thickening, and mediastinal emphysema. The lesions were regarded as of lower predominance if they were located below the inferior pulmonary vein. The HRCT patterns were then classified as NSIP, OP, NSIP with OP overlap (NSIP+OP), DAD and UIP in accordance with previous reports.[17] Patterns that could not be classified as those listed above were categorised collectively as unclassifiable pattern. Other types were defined as ILDs that were uncommon in anti-MDA5+DM, such as lymphocytic interstitial pneumonia.

Pathological analysis

Patients with qualified lung specimens were enrolled for lung histopathological analysis. The qualified specimens were those obtained by transbronchial lung biopsy (TBLB) with more than four tissues and a total area greater than 6 mm^2 or those with more than two tissues and the shortest length greater than 8 mm obtained by percutaneous lung biopsy (PLB). All lung specimens were stained with H&E and Elastica van Gieson stains and were independently reviewed by two experienced lung pathologists who were blinded to the clinical information. Disagreements between the two pathologists were discussed until a consensus was reached. The histopathological patterns were classified in accordance with the American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonia published in 2002 and updated in 2013.[17]

Statistical analysis

SPSS software (V.27.0) and GraphPad Prism software (V.6.0; San Diego, California, USA) were used in the statistical analysis. Data are expressed as mean±SD,

Table 1 Characteristics of patients with anti-MDA5+DM

Variable	Total (N=329)
General characteristics	
Age at initial visit, mean±SD, years	48.6±11.5
Female, n (%)	219 (66.6)
Smoking history, n (%)	53 (16.1)
Malignancy, n (%)	12 (3.6)
Disease duration, median (IQR), months	3.5 (2.0, 7.0)
ILD, n (%)	308 (93.6)
RPILD, n (%)	177 (53.8)
Pulmonary infection, n (%)	216 (65.7)
Clinical features at initial visit	
Heliotrope rash, n (%)	245 (74.5)
Gottron's sign, n (%)	270 (82.1)
Mechanic's hand, n (%)	182 (55.3)
Distal digital tip ulceration, n (%)	91 (27.7)
V sign, n (%)	165 (50.2)
Shawl sign, n (%)	127 (38.6)
Myalgia, n (%)	141 (42.9)
Muscle weakness, n (%)	197 (59.9)
Fever, n (%)	166 (50.5)
Laboratory findings	
Creatine kinase, median (IQR), IU/L	51.0 (25.0, 116.0)
Lymphocyte count, median (IQR), $\times 10^9$/L	0.73 (0.50, 1.04)
Lactate dehydrogenase, median (IQR), IU/L	308.0 (254.8, 399.3)
Ferritin*, median (IQR), ng/mL	590.5 (256.2, 1169.9)
Anti-Ro-52 antibody-positive, n (%)	206 (62.6)

*Data were available for 314 patients.
Anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; ILD, interstitial lung disease; RPILD, rapidly progressive ILD.

median (IQR) or number (percentage). Comparisons between groups were performed using the independent-sample t-test or Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Agreements between radiological and pathological diagnosis were assessed by kappa (k) coefficients. According to Landis and Koch's[18] guiding principles, k coefficients of 0.81–1, 0.61–0.80, 0.41–0.60, 0.21–0.40 and <0.20 are considered almost perfect, substantial, moderate, fair and poor, respectively. All analyses were two-tailed and p values <0.05 were considered to indicate statistical significance.

RESULTS

Demographic and clinical characteristics

The study enrolled 329 patients with anti-MDA5+DM, and their baseline clinical data are presented in table 1. The average age of disease onset was 48.6 years, and there was a male to female ratio of 1:2. The median disease duration was 3.5 months. Almost all patients (93.6%) presented with ILD, and more than half (53.8%) were classified as having RPILD. Along with ILD, other commonly observed clinical manifestations included heliotrope rash (74.5%) and Gottron's sign (82.1%). In addition, pulmonary infection was also frequently observed (65.7%).

OP was the primary radiographic pattern in anti-MDA5+DM

In anti-MDA5+DM, the predominant HRCT findings of the 329 patients were GGO (75.7%) and consolidation (64.4%) (figure 1A and online supplemental table S1). Reticulation (55.3%) was also common among them. In contrast, traction bronchiectasis (17.0%), honeycombing (2.7%), emphysema (5.5%), cysts (2.7%) and swollen mediastinal lymph nodes (12.2%) were less frequently observed. Mediastinal emphysema, a prognostic indicator of severe condition, was found in 30 (9.1%) patients.

We then differentiated the radiological patterns of these patients with reference to previous reports.[17] We found that OP (43.2%) was the primary radiographic pattern, followed by NSIP (26.4%), NSIP+OP (18.5%), unclassifiable pattern (2.1%), DAD (1.5%) and UIP (0.6%) (figure 1B and online supplemental table S1). Four patients had other radiographic patterns, three of which were consistent with lymphocytic interstitial pneumonia and one with lymphangioleiomyomatosis. The remaining 21 (6.4%) individuals did not have ILD and showed normal images.

A summary of the clinical characteristics and treatment strategies of patients with anti-MDA5+DM with different HRCT patterns is provided in table 2. Patients with NSIP+OP pattern had a shorter time from disease onset to ILD diagnosis and earlier initiation of treatment compared with those with NSIP or OP patterns (all adjusted p<0.05). Furthermore, patients with NSIP+OP or DAD patterns had higher levels of serum LDH and ferritin, as well as greater rates of intensive care unit (ICU) admission, mechanical ventilation and extracorporeal membrane oxygenation application and higher 12-month mortality compared with those with NSIP or OP patterns (all adjusted p<0.05).

NSIP and NSIP+OP were the primary histopathological patterns in anti-MDA5+DM

Of the 329 patients, 17 of whom we analysed had sufficiently large lung specimens (table 3). Microscopically, 15 cases showed homogeneous widened alveolar septa, interstitial fibrous hyperplasia, or infiltration of lymphocytes and plasma cells with no or minimal architectural distortion, which is consistent with the NSIP pattern. Among them, there was one case (6.7%) of cellular NSIP, seven cases (46.6%) of fibrotic NSIP and seven cases (46.6%) of mixed NSIP. Focal OP was observed in eight of them. Considering the small size of specimens taken by TBLB and PLB, it was difficult to estimate the proportion of OP, so these eight patients were designated as

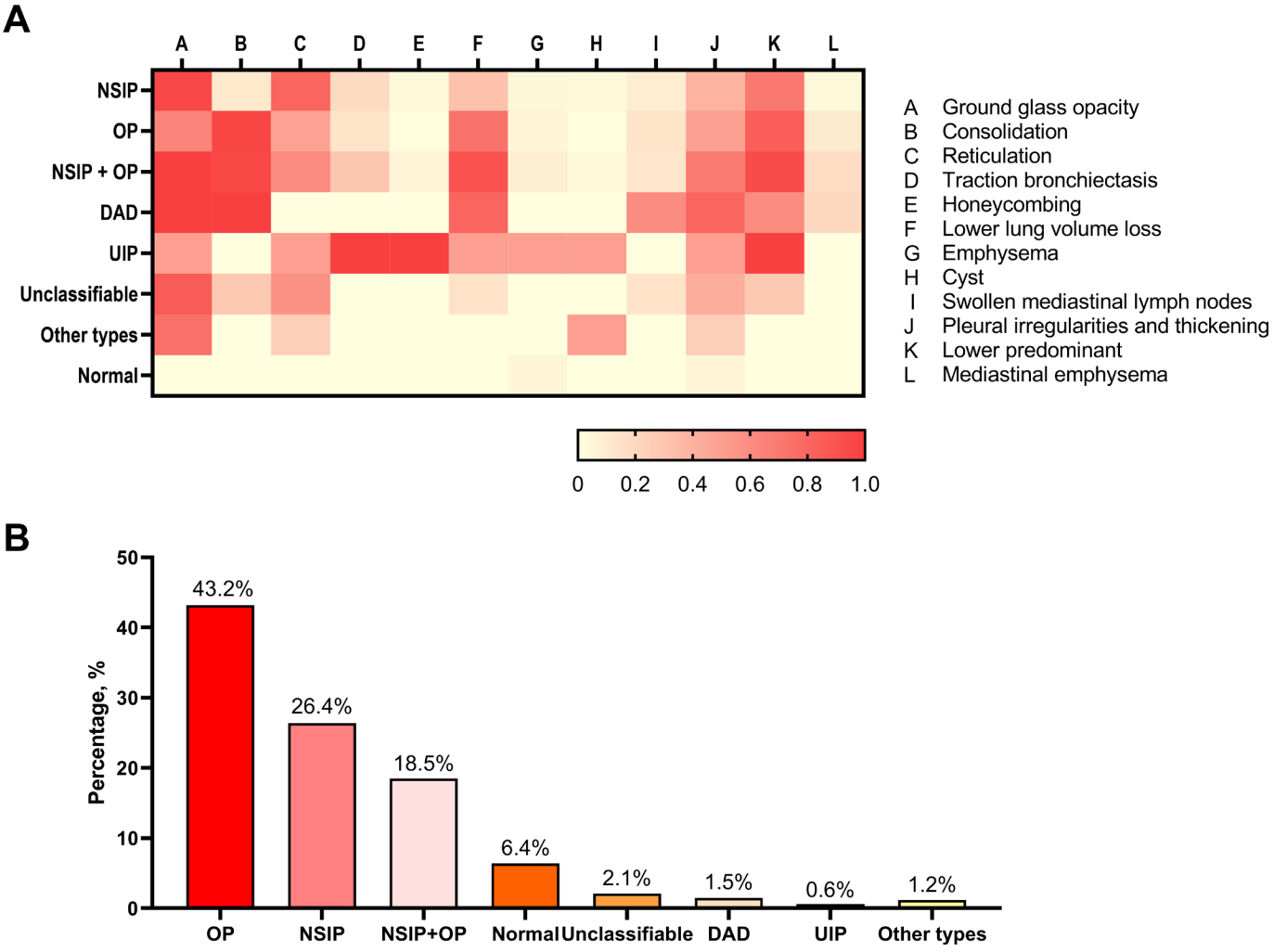

Figure 1 Radiological analysis of patients with anti-MDA5+DM. (A) Distribution of HRCT findings in various radiographic patterns in anti-MDA5+DM. (B) Distribution of radiographic patterns of ILD in 329 patients with anti-MDA5+DM. Anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; DAD, diffuse alveolar damage; HRCT, high-resolution CT; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; UIP, usual interstitial pneumonia.

having an NSIP+OP pattern (47.1%). In addition, there was one case of alveolar hyaline membrane formation (figure 2E') and one case consistent with acute fibrin OP (figure 2F').

Poor consistency between radiological and histopathological diagnosis of anti-MDA5+DM ILD

According to the above results, we found that the proportion of the OP pattern in anti-MDA5+DM varied greatly in imaging and pathology, which prompted us to analyse the consistency of radiology and pathology of these 17 patients. Table 4 depicts the level of agreement between radiological and histopathological diagnoses in anti-MDA5+DM. We found that only two patients had the same radiological and histopathological diagnosis, both with NSIP+OP pattern, whereas the results were inconsistent among the other patients. The diagnostic coincidence rate was only 11.8%, and the k statistics indicated poor agreement between the two diagnostic methods (weighted kappa=−0.098, 95% CI −0.325 to 0.128). Representative radiological and histopathological images are shown in figure 2.

Radiological and histopathological differences between RPILD and non-RPILD in anti-MDA5+DM

According to the clinical onset forms of ILD, patients were divided into the RPILD group and the non-RPILD group. As shown in table 5, we found that OP remained the predominant radiographic pattern in both the RPILD and non-RPILD groups, and there was no significant difference between the two groups (44.6% vs 48.1%, p=0.547). However, NSIP+OP was more common in the RPILD group than in the non-RPILD group (26.6% vs 10.7%, p=0.001), whereas NSIP was less common in the RPILD group (21.5% vs 37.4%, p=0.002).

Unlike imaging diagnosis, pathological analysis of the 17 patients with qualified lung specimens revealed that the majority of the patients in the non-RPILD group showed the NSIP pattern (6/10, 60%). The RPILD group showed various histopathological patterns, including

Table 2 Baseline characteristics of patients with anti-MDA5+DM with different HRCT patterns

Parameters	NSIP (n=87, group 1)	OP (n=142, group 2)	NSIP+OP (n=61, group 3)	UIP (n=2, group 4)	DAD (n=5, group 5)	Unclassifiable (n=7, group 6)	Other types (n=4, group 7)	Adjusted p value (pairwise comparison of the groups)
General characteristics								
Age, median (IQR), years	49.0 (41.0, 56.0)	48.0 (40.0, 57.3)	54.0 (49.5, 59.0)	62.5 (57.0, *)	56.0 (45.0, 63.5)	54.0 (39.0, 67.0)	45.0 (35.3, 55.5)	NS
Female, n (%)	54 (62.1)	107 (75.4)	38 (62.3)	0 (0.0)	4 (80.0)	7 (100.0)	3 (75.0)	NS
Smoking history, n (%)	17 (19.5)	15 (10.6)	12 (19.7)	1 (50.0)	1 (20.0)	0 (0.0)	0 (0.0)	NS
Malignancy, n (%)	2 (2.3)	3 (2.1)	5 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NS
Disease duration, median (IQR), months	4.0 (2.0, 8.0)	4.0 (2.0, 7.0)	2.0 (1.0, 4.5)	5.5 (2.0, *)	4.0 (2.0, 6.5)	4.0 (3.0, 6.0)	1.8 (0.9, 2.0)	NS
Disease onset to ILD diagnosis, median (IQR), months	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	1.0 (1.0, 1.8)	5.0 (2.0, *)	2.0 (1.0, 3.5)	4.0 (1.0, 6.0)	0.9 (0.6, 1.8)	<0.05 (groups 1–3) <0.05 (groups 2–3)
Disease onset to initial treatment, median (IQR), months	2.0 (1.0, 3.0)	2 (1.0, 3.0)	1.0 (1.0, 2.0)	5.0 (2.0, *)	1.0 (1.0, 3.0)	4.0 (1.0, 6.0)	0.9 (0.6, 1.8)	0.006 (groups 1–3) 0.011 (groups 2–3)
RPILD, n (%)	38 (43.7)	79 (55.6)	47 (77.0)	2 (100.0)	5 (100.0)	4 (57.1)	2 (50.0)	<0.05 (groups 1–3)
Pulmonary infection, n (%)	51 (58.6)	98 (69.0)	47 (77.0)	2 (100.0)	4 (80.0)	6 (85.7)	3 (75.0)	NS
Clinical features at initial visit								
Heliotrope rash, n (%)	67 (77.0)	116 (81.7)	35 (57.4)	2 (100.0)	2 (40.0)	4 (57.1)	3 (75.0)	<0.05 (groups 2–3)
Gottron's sign, n (%)	74 (85.1)	118 (83.1)	51 (83.6)	2 (100.0)	2 (40.0)	6 (85.7)	2 (50.0)	NS
Mechanic's hand, n (%)	48 (55.2)	78 (54.9)	38 (62.3)	1 (50.0)	0 (0.0)	4 (57.1)	2 (50.0)	NS
Distal digital tip ulceration, n (%)	20 (23.0)	49 (34.5)	15 (24.6)	0 (0.0)	1 (20.0)	1 (14.3)	2 (50.0)	NS
V sign, n (%)	43 (49.4)	79 (55.6)	27 (44.3)	1 (50.0)	1 (20.0)	2 (28.6)	2 (50.0)	NS
Shawl sign, n (%)	32 (36.8)	61 (43.0)	19 (31.1)	1 (50.0)	1 (20.0)	2 (28.6)	1 (25.0)	NS
Myalgia, n (%)	36 (41.4)	67 (47.2)	17 (27.9)	2 (100.0)	2 (40.0)	6 (85.7)	2 (50.0)	<0.05 (groups 3–6)
Muscle weakness, n (%)	55 (63.2)	85 (59.9)	31 (50.8)	2 (100.0)	1 (20.0)	7 (100.0)	4 (100.0)	NS
Fever, n (%)	47 (54.0)	63 (44.4)	40 (65.6)	2 (100.0)	5 (100.0)	4 (57.1)	1 (25.0)	NS
Laboratory findings								
Creatine kinase, median (IQR), IU/L	35.5 (23.0, 126.3)	52.5 (28.0, 109.3)	48.0 (24.0, 107.8)	92.5 (58.0, *)	111.0 (44.0, 181.0)	68.0 (21.0, 115.0)	150.5 (47.8, 423.5)	NS

Continued

Table 2 Continued

Parameters	NSIP (n=87, group 1)	OP (n=142, group 2)	NSIP+OP (n=61, group 3)	UIP (n=2, group 4)	DAD (n=5, group 5)	Unclassifiable (n=7, group 6)	Other types (n=4, group 7)	Adjusted p value (pairwise comparison of the groups)
Lymphocyte count, median (IQR), $\times 10^9$/L	0.79 (0.53, 1.06)	0.74 (0.48, 0.93)	0.66 (0.51, 0.94)	0.56 (0.54, *)	0.45 (0.15, 0.72)	0.60 (0.30, 0.70)	0.73 (0.47, 1.46)	NS
Lactate dehydrogenase, median (IQR), IU/L	290.0 (235.0, 378.0)	301.5 (254.0, 357.5)	359.5 (284.5, 492.0)	273.0 (267.0, *)	667.0 (514.5, 840.5)	483.0 (316.0, 654.0)	374.0 (282.5, 502.3)	0.014 (groups 1–3) 0.009 (groups 2–3) 0.008 (groups 1–5) 0.009 (groups 2–5)
Ferritin, median (IQR), ng/mL	456.8 (208.8, 1078.4)	553.5 (173.4, 1151.9)	993.3 (658.1, 1923.0)	1007.7 (886.8, *)	978.6 (365.7, 3349.3)	551.6 (158.7, 1005.0)	569.8 (292.6, 2181.5)	0.001 (groups 1–3) 0.002 (groups 2–3)
Anti-Ro-52 antibody-positive, n (%)	55 (63.2)	89 (62.7)	46 (75.4)	2 (100.0)	3 (60.0)	3 (42.9)	3 (75.0)	NS
Treatment after admission								
Steroid used, n (%)	86 (98.9)	140 (98.6)	60 (98.4)	2 (100.0)	4 (80.0)	7 (100.0)	4 (100.0)	NS
PMT, n (%)	5 (5.7)	8 (5.6)	7 (11.5)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	NS
Immunosuppressant used, n (%)	79 (90.8)	123 (86.6)	45 (73.8)	2 (100.0)	3 (60.0)	6 (85.7)	2 (50.0)	NS
CYC	14 (16.1)	11 (7.7)	3 (4.9)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	NS
CNI	54 (62.1)	102 (71.8)	40 (65.6)	1 (50.0)	2 (40.0)	3 (42.9)	2 (50.0)	NS
MMF	7 (8.0)	7 (4.9)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NS
JAKi	10 (11.5)	12 (8.5)	5 (8.2)	0 (0.0)	1 (20.0)	2 (28.6)	0 (0.0)	NS
Biological agents	3 (3.4)	7 (4.9)	6 (9.8)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	NS
Total number of immunosuppressant ≥2, n (%)	33 (37.9)	38 (26.8)	16 (26.2)	0 (0.0)	1 (20.0)	3 (42.9)	0 (0.0)	NS
IVIG, n (%)	24 (27.6)	51 (35.9)	26 (42.6)	0 (0.0)	3 (60.0)	1 (14.3)	1 (25.0)	NS
ICU admission, n (%)	7 (8.0)	10 (7.0)	15 (24.6)	0 (0.0)	5 (100.0)	2 (28.6)	1 (25.0)	<0.05 (groups 2–3) <0.05 (groups 1–5) <0.05 (groups 2–5) <0.05 (groups 3–5)

Continued

Table 2 Continued

Parameters	NSIP (n=87, group 1)	OP (n=142, group 2)	NSIP+OP (n=61, group 3)	UIP (n=2, group 4)	DAD (n=5, group 5)	Unclassifiable (n=7, group 6)	Other types (n=4, group 7)	Adjusted p value (pairwise comparison of the groups)
Mechanical ventilation, n (%)	6 (6.9)	12 (8.5)	17 (27.9)	0 (0.0)	5 (100.0)	2 (28.6)	1 (25.0)	<0.05 (groups 1–3) <0.05 (groups 1–5) <0.05 (groups 2–3) <0.05 (groups 2–5) <0.05 (groups 3–5)
VV-ECMO, n (%)	0 (0.0)	2 (1.4)	1 (1.6)	0 (0.0)	3 (60.0)	0 (0.0)	0 (0.0)	<0.05 (groups 1–5) <0.05 (groups 2–5) <0.05 (groups 3–5)
Lung transplantation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NS
12-month mortality	12 (13.8)	27 (19)	28 (45.9)	0 (0.0)	5 (100.0)	2 (28.6)	1 (25.0)	<0.05 (groups 1–3) <0.05 (groups 2–3) <0.05 (groups 1–5) <0.05 (groups 2–5)

*Incomplete data due to small number of cases in the UIP group.
Anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; CNI, calcineurin inhibitors; CYC, cyclophosphamide; DAD, diffuse alveolar damage; HRCT, high-resolution CT; ICU, intensive care unit; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; JAKi, Janus kinase inhibitors; MMF, mycophenolate mofetil; NS, no significance; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; PMT, pulse methylprednisolone therapy; RPILD, rapidly progressive interstitial lung disease; UIP, usual interstitial pneumonia; VV-ECMO, venovenous extracorporeal membrane oxygenation.

Table 3 Histopathological pattern of patients with anti-MDA5+DM

Variable	n=17
Histopathological pattern, n (%)	
NSIP pattern	7 (41.2)
OP pattern	0 (0.0)
NSIP+OP pattern	8 (47.1)
DAD pattern	1 (5.9)
AFOP pattern	1 (5.9)
All cases with NSIP pattern*, n (%)	
Cellular NSIP pattern	1 (6.7)
Fibrotic NSIP pattern	7 (46.6)
Mixed NSIP pattern	7 (46.6)

*Only patients with NSIP were included (n=15).
AFOP, acute fibrinous and organising pneumonia; anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; DAD, diffuse alveolar damage; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia.

NSIP+OP (57.1%), NSIP (14.3%), DAD (14.3%) and acute fibrinous and organising pneumonia (AFOP) (14.3%).

DISCUSSION

This study aimed to analyse the radiological and histopathological features of anti-MDA5+DM ILD. A retrospective analysis of 329 patients with anti-MDA5+DM revealed that a vast majority (93.6%) had developed ILD. OP was found to be the predominant radiographic pattern, while NSIP and NSIP+OP were the prominent histopathological patterns. However, there was poor correlation between the radiological category of ILD and the histopathological assessment, especially in patients presenting with OP on HRCT. In the RPILD group, radiographic NSIP+OP was more common than in the non-RPILD group, while NSIP was less frequently observed. These findings highlight the importance of integrating both radiological and histopathological approaches for accurate diagnosis and

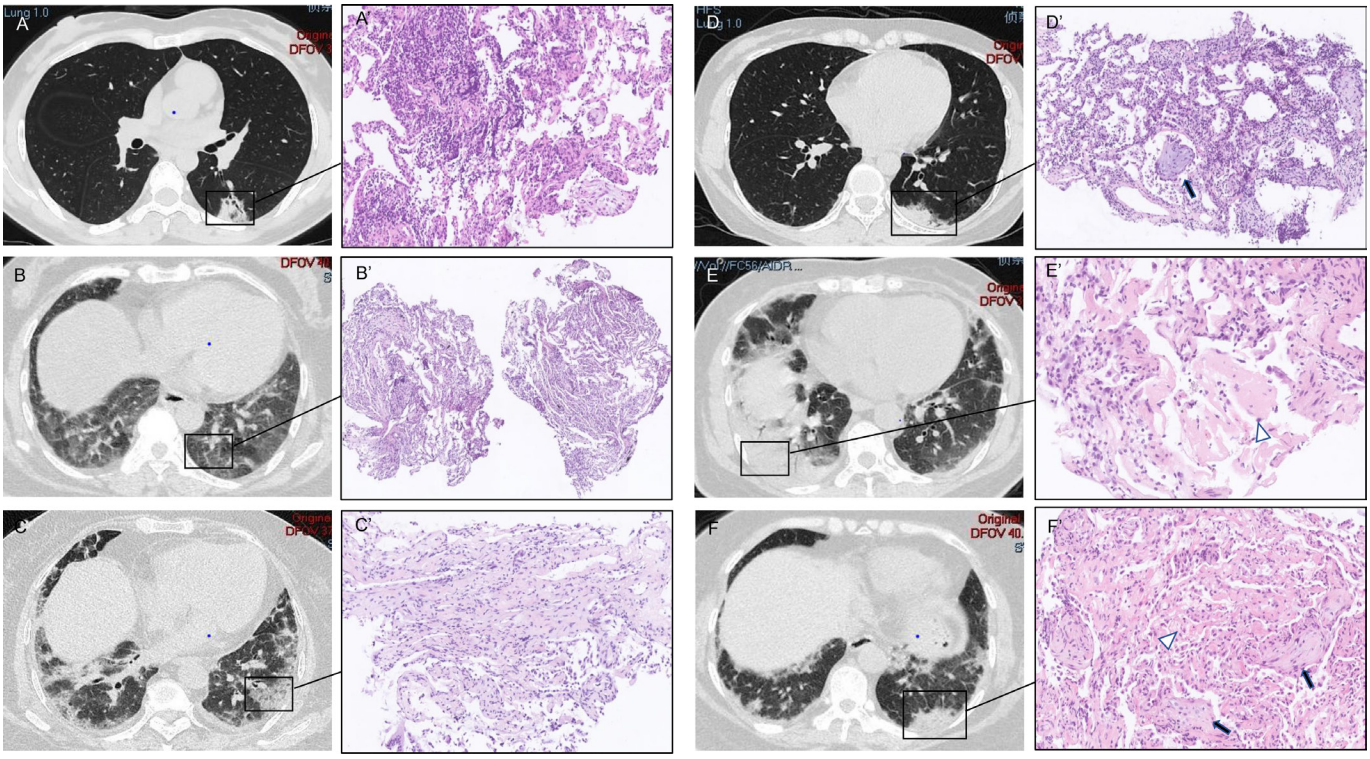

Figure 2 Radiological and histopathological images of patients with anti-MDA5+DM ILD. (A, A') Case 1 showed subpleural consolidation on HRCT, but showed extensive lymphocyte and plasma cell infiltration and preserved lung tissue structure on pathology, consistent with cellular NSIP. (B, B') Case 2 showed extensive GGO on HRCT, and pathology showed homogeneous alveolar septa widening, interstitial fibrous hyperplasia, and lymphocyte and plasma cell infiltration without OP, consistent with mixed NSIP. (C, C') Case 3 showed GGO and consolidation on HRCT and extensive fibrous hyperplasia on pathology. (D, D') Case 4 showed OP on HRCT, but showed focal OP (arrow) superimposed on a background of NSIP pathologically. (E, E') Case 5 showed extensive consolidation on HRCT, but the alveoli (white arrowhead) showed hyaline membrane formation, leading to the diagnosis of DAD. (F, F') Case 6 showed subpleural consolidation on HRCT, but pathologically showed fibrin (white arrowhead) mixed with OP (arrows), consistent with AFOP. Magnification: ×40 (B'), ×100 (A', C', D', E'), ×150 (F') (H&E). See table 3 for other definitions. AFOP, acute fibrinous and organising pneumonia; anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; DAD, diffuse alveolar damage; GGO, ground-glass opacity; HRCT, high-resolution CT; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia.

Table 4 Consistency in the radiological and histopathological diagnosis of anti-MDA5+DM ILD

Radiological pattern	Histopathological pattern					Total
	NSIP	OP	NSIP+OP	DAD	AFOP	
NSIP	0	0	1	0	0	1
OP	4	0	5	0	1	10
NSIP+OP	3	0	2	1	0	6
Total	7	0	8	1	1	17

% agreement: 11.8%; kw=−0.098 (95% CI −0.325 to 0.128), p=0.416.
% agreement was calculated by adding the concordant percentages.
See table 2 for other definitions.
AFOP, acute fibrinous and organising pneumonia; anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; DAD, diffuse alveolar damage; ILD, interstitial lung disease; kw, weighted kappa; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia.

management of this disease, as anti-MDA5+DM ILD is associated with significant mortality.

Previously, NSIP was considered the most common radiographic pattern in IIM.[7] However, IIM is a highly heterogeneous group of disorders, with each subgroup having a unique phenotype. Anti-MDA5+DM showed diverse radiographic patterns, yet without consensus on the predominant pattern to date. Hozumi *et al*[19] described the most predominant HRCT pattern in anti-MDA5+DM as 'unclassifiable', which was not typical of pure NSIP, OP or UIP. In contrast, Shao *et al*[20] and our previous study[10] considered OP to be the primary radiographic pattern in anti-MDA5+DM. This discrepancy might be caused by different cohorts or sample sizes. Consistent with the latter, the present study demonstrated in a larger cohort that patchy consolidation (64.4%) and GGO (75.7%) were the two main HRCT findings in patients with anti-MDA5+DM, mainly in the subpleural and basilar areas, and OP (43.2%) was the dominant radiographic pattern, followed by NSIP, NSIP+OP, unclassifiable pattern, DAD and UIP.

Table 5 Relationship between ILD patterns and clinical course in patients with anti-MDA5+DM

Variables	RPILD	Non-RPILD	P value
Radiological pattern, n (%)*			
NSIP	38 (21.5)	49 (37.4)	**0.002**
OP	79 (44.6)	63 (48.1)	0.547
NSIP+OP	47 (26.6)	14 (10.7)	**0.001**
DAD	5 (2.8)	0 (0.0)	0.074
UIP	2 (1.1)	0 (0.0)	0.510
Unclassifiable pattern	4 (2.3)	3 (2.3)	1.000
Other types	2 (1.1)	2 (1.5)	1.000
Histopathological pattern, n (%)†			
NSIP	1 (14.3)	6 (60.0)	–
OP	0 (0.0)	0 (0.0)	–
NSIP+OP	4 (57.1)	4 (40.0)	–
DAD	1 (14.3)	0 (0.0)	–
AFOP	1 (14.3)	0 (0.0)	–

*Data available for 308 patients.
†Data available for 17 patients.
AFOP, acute fibrinous and organising pneumonia; anti-MDA5+DM, anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis; DAD, diffuse alveolar damage; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; RPILD, rapidly progressive interstitial lung disease; UIP, usual interstitial lung disease.

Video-assisted thoracoscopic surgery and open lung biopsy (often collectively referred to as 'surgical lung biopsy') are the recommended methods to assist in the diagnosis of ILD because these methods provide a relatively large amount of lung tissue to reveal lung pathology. However, they are difficult to conduct widely in clinical practice due to their invasive nature and potential for acute exacerbation of ILD, especially in anti-MDA5+DM.[21 22] Our study analysed lung specimens from 17 patients with anti-MDA5+DM and found that NSIP (41.2%) and NSIP+OP (47.1%) were the predominant histopathological patterns. Further analysis showed that fibrotic NSIP and mixed NSIP were the two main histological subtypes, suggesting the presence of varying degrees of pulmonary fibrosis. Therefore, early initiation of antifibrotic therapy may be effective in such patients. This conclusion is supported by the findings of Li *et al*,[23] who found that patients with subacute ILD benefited most from pirfenidone. To our knowledge, the present study is the largest series in the medical literature investigating lung pathology in patients with anti-MDA5+DM.

Intriguingly, the coincidence rate of radiographic diagnosis and pathological diagnosis of ILD pattern in anti-MDA5+DM was very low, with only 11.8%. Specifically, 9 of the 17 patients showed radiographic OP with a corresponding pathological pattern of NSIP or NSIP+OP. Microscopically, numerous lymphocytes and plasma cells infiltrated the lung interstitium, accompanied by fibrous tissue proliferation. This is different from cryptogenic OP,[24 25] which has only a small amount of inflammatory cell infiltration in the interstitium of the lung, without obvious interstitial fibrous tissue

proliferation. An explanation for this phenomenon could be attributed to anti-MDA5+DM, a connective tissue disorder that causes pathological OP as a secondary feature in the context of NSIP. Therefore, caution must be exerted when interpreting the imaging, and HRCT patterns cannot be directly transposed into histological considerations.

Clinically, the radiographic pattern of anti-MDA5+DM ILD correlated significantly with the clinical course. Our study revealed that OP remained the predominant radiographic pattern in both the RPILD group (44.6%) and the non-RPILD group (48.1%). NSIP+OP was more common in patients with RPILD, whereas NSIP was less observed. This result indicates that clinicians should exercise extreme vigilance to monitor for rapid disease progression when they encounter radiographic patterns of NSIP+OP. Despite the limited number of lung biopsy samples, we could not draw a firm conclusion on the pathological differences between the two groups. However, our study adds that patients with pathological NSIP, NSIP+OP or AFOP patterns, in addition to DAD which is known to lead to acute exacerbations,[26] can also develop RPILD.

Previous studies have suggested that patients with anti-MDA5+DM have an unfavourable prognosis, which is associated with certain factors such as advanced age and elevated levels of serum ferritin, LDH and neutrophil to lymphocyte ratio.[27–31] Our study results demonstrated that patients with radiological patterns of NSIP+OP or DAD have a higher risk of poor prognosis due to consequential factors such as high serum ferritin and LDH levels, frequent ICU admissions, and more invasive procedures. Consequently, using HRCT patterns in conjunction with other clinical indicators could enable clinicians to more effectively assess patient prognosis. Since chest HRCT patterns in anti-MDA5+DM may change over time, future longitudinal cohort studies with larger sample sizes are necessary to investigate these alterations.

This study had several limitations that should be acknowledged. First, this was a single-centre retrospective study, and intrinsic bias could not be avoided completely. Second, the presence of infection complications was not excluded, and therefore it is necessary to take into consideration whether patients had any infections when interpreting radiological and histopathological features. Third, the lung specimens obtained by PLB and TBLB were relatively small, resulting in a poor representation of histological samples in some cases. Fourth, other rare patterns of ILD were not described in detail in this study due to the scarcity of relevant cases. Finally, we only selected HRCT images from patients during their initial hospital admission, which primarily reflects the early stages of the disease course, and consequently radiographic features of patients in the later disease stages were outside the scope of this article.

CONCLUSIONS

The study showed that RPILD was a typical feature of anti-MDA5+DM. OP was the predominant radiographic pattern, and its corresponding pathological pattern was NSIP or NSIP+OP. Radiographic NSIP pattern was mainly found in the non-RPILD group, whereas NSIP+OP may clinically predict RPILD. In addition, patients with radiographic NSIP+OP or DAD had more risk factors for poor prognosis.

Familiarity with the unique clinical, radiological and pathological features of anti-MDA5+DM ILD may help elucidate its underlying pathophysiological mechanisms and disease behaviour in the future.

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