Interstitial lung disease in adult patients with anti-NXP2 antibody positivity: a multicentre 18-month follow-up study

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Abstract

Objective

Anti-nuclear matrix protein 2 (NXP2) antibody is a rare myositis-specific antibody. Thus, the pattern and prognosis of interstitial lung disease (ILD) in NXP2-positive patients remain unclear. This study investigates the clinical features and effects of pulmonary complications on survival in NXP2-positive patients.

Methods

We retrospectively analysed the clinical and follow-up data of a cohort of 33 hospitalised adult patients with anti-NXP2 antibody positivity at three tertiary rheumatology centres from June 2017 to December 2020.

Results

Thirty-three patients were enrolled, and 87.9% (29/33) had dermatomyositis. The major pulmonary lesions manifested as various types of ILD (14/33, 42.4%), bilateral pleural effusion (2/33, 6.1%) and diffuse alveolar haemorrhage (1/33, 3%). Only 3 patients (3/33, 9.1%) had respiratory symptoms at onset. The most common lung imaging manifestations were non-specific interstitial pneumonia (NSIP) and/or organising pneumonia (OP) (11/14, 78.6%). Patients in the ILD group were older than those in the non-ILD group (p=0.002). Logistic regression analysis showed that age (p=0.008) was the only independent predictor for ILD. Kaplan-Meier survival curves displayed no association between ILD and all-cause death (log-rank p=0.84). None of the deaths during follow-up were directly related to ILD.

Conclusion

Adult patients with anti-NXP2 antibody positivity mainly had dermatomyositis. Concurrent ILD is not uncommon, but clinical manifestations are often latent. NSIP and/or OP are the most common patterns. ILD is more common in older age groups. Although the prognosis of patients in the ILD group is not very poor, early screening may help to improve prognosis and quality of life.

Key words

NXP2, anti-nuclear matrix protein 2 antibody, dermatomyositis, interstitial lung disease, high-resolution computed tomography

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Received on February 18, 2022; accepted in revised form on May 9, 2022.

Funding: this research was supported by The Second Affiliated Hospital of Jiaxing University Hospital level Foundation no.Y2021-Y107.

Competing interests: none declared.

Introduction

Idiopathic inflammatory myopathies (IIMs) are heterogeneous disorders characterised by muscle inflammation and frequently accompanied by extramuscular manifestations that affect the skin and lungs. There is increasing recognition of antibodies specific for IIMs; myositis-specific antibodies (MSAs) are clinically useful biomarkers that aid in the diagnosis of distinct clinical phenotypes (1, 2). Among these MSAs, the anti-nuclear matrix protein 2 (NXP2) antibody is a rare antibody of typical dermatomyositis (DM) (3), although the characteristic rash may not be detected at the time of antibody detection (4). Interstitial lung disease (ILD) is a common complication of DM, and anti-NXP2 antibody positivity in adult patients have been reported, with prevalences ranging from 0% to 26.8% (5-7). A systematic review and meta-analysis reported the risk of ILD was significantly reduced in NXP2-positive DM patients (odds ratio (OR) 0.26, 95% confidence interval (CI), 0.18–0.38, $p<0.001$) (8). However, it must be noted that the control group for this OR value had the another type of DM, MDA5-positive DM, which is not a normal population (*e.g.* anti-MDA5 antibody). Because of the rarity of anti-NXP2-positive dermatomyositis, studies on lung involvement associated with anti-NXP2 antibodies are rare. Only a few case-cohort studies or few case reports have focused on pulmonary involvement in NXP2-positive dermatomyositis (9, 10). However, despite its rarity, ILD still has a significant impact on the available treatment options for these patients, as well as their prognosis and quality of life. So further analysis the clinical, serological, and radiological features of ILD in NXP2-positive patients are necessary to achieve better management of these patients and to improve their prognosis.

Materials and methods

Patients

This is a retrospective, triple-centre, case-control study. We performed a retrospective analysis of a cohort of 33 hospitalised adult patients with anti-NXP2 antibody positivity in three tertiary rheumatology centres in China from June 2017 to 2020. We selected all rheumatic patients with positive anti-NXP2 antibodies recorded in electronic medical records who were either diagnosed with IIMs or screened for myositis antibodies due to ILD of unknown origin. None of the three rheumatology centres accepts children younger than 16 years of age, but the cohort included patients with an age at onset of less than 16 at inclusion. We excluded patients who had a +/- anti-NXP2 titre and did not satisfy the classification criteria for DM (11).

Definition of clinical data

Some definitions are detailed as follows. Disease duration was defined as the time from symptom onset to baseline. Age of onset was defined as the age at which symptoms were first experienced. The diagnosis of immune-mediated necrotising myositis (INMN) requires pathological confirmation with an excisional muscle biopsy. Smoking was defined as consuming at least one cigarette per day for at least 3 months, and a lower quantity was defined as non-smoking. Concomitant malignancies were defined as the time from 3 years before diagnosis to the date of the last follow-up (December 2021). The creatinine kinase (CK) peak was defined as the highest serum CK level documented in the medical record at any stage of the disease. Finally, all ILD patients who met the inclusion criteria were selected as the research group, and other patients were included in the control group. Demographic information, clinical characteristics, laboratory data, and high-resolution computed tomography (HRCT) were obtained through a review of the medical records. The last date of follow-up was December 2021 to determine the survival time and cause of death for all patients who had a follow-up period of at least 18 months.

Due to the retrospective nature of the study, we were granted a waiver of written informed consent but obtained verbal informed consent from all patients by telephone. Ethics approval was obtained from the respective Ethics Committees.

Autoantibody detection

Serum samples from every patient were tested for autoimmune inflammatory myopathy antibodies by a commercial line blot assay, and the results were recorded in detailed electronic medical records. Each strip of the assay contained 16 autoantigens (NXP2, MDA5, TIF1γ, Mi-2α, Mi-2β, SAE, SRP, Jo-1, OJ, EJ, PL-7, PL-12, Ku, PM-Scl75, PM-Scl100, and Ro52) and was performed by using a EUROLINE autoimmune inflammatory myopathies Ag (IgG) test kit (EUROIMMUN, Germany) according to the manufacturer's instructions. Finally, immunopositive bands were scanned and qualitatively defined as -, +, ++, and +++. Occasionally, expression of +- was observed.

HRCT and ILD

HRCT was performed at baseline, which generally occurred during hospitalisation or within 1 month prior to admission. ILD was diagnosed based on HRCT, and pulmonary function (forced vital capacity (FVC)%, carbon monoxide diffusing capacity (DLCO)%, etc.) was included as an important reference index for ILD evaluation. Subjects with pulmonary HRCT imaging were normal, and pulmonary function manifested a small change in FVC% or DLCO%, which were classified as the Non-ILD group. This is helpful in summarising lung imaging findings. This may have led to imprecision but did not affect the results. Distinguishing clearly between ILD, infection-triggered ILD and pulmonary infection is sometimes difficult in the context of IIM disease and immunosuppressive therapy. Therefore, patients with infection were not systematically excluded. HRCT scan patterns were classified as definite UIP, probable UIP, non-UIP, non-specific interstitial pneumonia (NSIP), and organising pneumonia (OP) on review by experienced radiologists according to the 2002 American Thoracic Society (ATS) and European Respiratory Society (ERS) policies, which were updated in 2013 by the ATS/ERS (12, 13). All HRCT images were reviewed by two observers (X.C. and Q.W., with 10 years of experience in chest HRCT imaging evaluation) who were blinded to the patient outcomes. When the opinions were inconsistent, a rheumatologist was involved.

Table I. General features of patients with anti-NXP2 positive antibodies.

Features	n (%) or median [IQR]
Disease	
Dermatomyositis, n (%)	29 (87.9)
Polymyositis, n (%)	2 (6.1)
IPAF, n (%)	1 (3)
INMN, n (%)	1 (3)
Gender	
Female, n (%)	24
Male, n (%)	9
Age at onset (years), Median [IQR]	44 [25, 54.5]
Age (years), Median [IQR]	45 [27.5, 54.5]
Tobacco smoking, n (%)	6 (18.2)
ILD, n (%)	14 (42.4)
Dysphagia, n (%)	17 (51.5)
Malignancy, n (%)	2 (6.1)
MSAs overlap	
Anti-EJ antibody positive, n (%)	1 (3)
Anti-SRP antibody positive, n (%)	1 (3)
Anti-MDA5 antibody positive, n (%)	1 (3)
Disease overlap	
SS, n (%)	3 (9.1)
PBC+SS, n (%)	1 (3)
RA+SS, n (%)	1 (3)
PBC, n (%)	1 (3)
Psoriasis, n (%)	1 (3)
HLH, n (%)	1 (3)

IRQ: interquartile range; IPAF: interstitial pneumonia with autoimmune features; INMN: immune-mediated necrotising myositis; ILD: interstitial lung disease; NXP2: nuclear matrix protein 2; MSAs: myositis-specific autoantibodies; SRP: signal recognition particle; MDA5: melanoma differentiation associated protein 5; SS: Sjögren's syndrome; PBC: primary biliary cholangitis; RA: rheumatoid arthritis; HLH: haemophagocytic lymphohistiocytosis.

Statistical analysis

Dichotomous variables are expressed as absolute frequencies (percentages) and were compared using Fisher's exact test. Continuous variables are described using medians [interquartile ranges (IQRs)], and statistical comparison between the groups was performed with the Mann-Whitney non-parametric U-test. Multivariate logistic regression analysis was conducted by fitting a logistic regression model, and the data shown were fitted with a second-order polynomial function. Survival analysis was estimated using the Kaplan-Meier method, and the differences between groups were assessed using the log-rank test. p-values <0.05 were considered indicative of statistical significance. All statistical calculations were performed using SPSS statistical software (IBM SPSS v. 19), and graphs were plotted with GraphPad Prism v. 8 software.

Results

Study population and characteristics

Thirty-three adult patients who had anti-NXP2 antibody positivity at the time of enrolment were included in the study. There were 24 females (72.7%) and 9 males (27.3%), with a mean age at inclusion of 45 [27.5, 54.5] years, ranging from 16 to 71 years. Twenty-four patients (72.7%) were included in the initial population, and the duration of disease was less than 6 months. Of these patients, 29 had DM (87.9%), 2 had polymyositis (6.1%), 1 had INMN (3%), and 1 had interstitial pneumonia with autoimmune features (IPAF) (3%). Except for 1 patient, IIMs were diagnosed for each patient before the respiratory assessment. Fourteen patients (42.4%) had ILD, and none of the patients presented any family history or environmental exposure. Only 3 patients (9.1%) had respiratory symptoms at onset. Despite MSAs being almost entirely mutually exclusive, we found 3 overlapping MSAs (anti-MDA5, EJ, and SRP antibodies). Of note, all of

these patients had ILD involvement. In addition, we found more overlap, with 8 of these patients (24.2%) overlapping with other rheumatic diseases. Sjögren's syndrome was found to occur with the highest frequency (n=5), followed by primary biliary cholangitis (PBC) (n=2). Patient data and characteristics are summarised in Table I.

Comparison of clinical features

The main clinical features of anti-NXP2 antibody-positive patients with and without ILD are compared. The comparison revealed significant differences between the two groups in age (p=0.002), age at onset (p=0.002), FVC% (p<0.001) and DLCO% (p<0.001). A trend toward elevation in some possible serologic biomarkers (serum ferritin (SF), lactate dehydrogenase (LDH), and anti-Ro52 antibody) of DM-ILD was apparent in the ILD group (14, 15), however differences between groups were not statistically significant. An additional change occurred in CRP (p=0.036). Table II shows the results of the two groups that were compared.

HRCT patterns

All patients had at least one valuable HRCT scan during the baseline hospitalisation. Thirty patients (90.9%) did not have any respiratory symptoms (cough or dyspnoea) at onset. The major pulmonary lesions manifested as various types of ILD (n=14), bilateral pleural effusion (n=2) and diffuse alveolar haemorrhage (DAH) (n=1). There was 1 case of lung cancer in a patient without ILD. Fourteen patients (42.4%) had differing degrees of ILD imaging changes in chest HRCT (Fig. 1), including NSIP (n=6) NSIP with OP (n=3), OP (n=2), probable UIP with NSIP (n=1), probable UIP with OP (n=1) and indeterminate (n=1). No definite UIP was found as a pattern of reticulation and honeycombing. There were no cases of rapidly progressive ILD. The various manifestations of pulmonary lesions are listed in Table III.

Predictor for ILD

Factors potentially associated with ILD were included in the logistic regression analysis to identify the most meaningful early predictors for ILD. Univariate regression analysis showed that age (OR=1.094, 95% CI: 1.023–1.171 p=0.009) was a significant predictor for ILD. Multivariate logistic regression analysis was used to adjust the effects of confounding factors such as sex and disease duration and showed that age (OR=1.119, 95% CI: 1.029–1.216 p=0.008) was the only independent predictive factor for ILD in anti-NXP2-positive DM. Furthermore, some possible serologic biomarkers (SF, LDH, and anti-Ro52 antibody) of DM-ILD did not exhibit predictive value (Table IV).

Survival analysis

All patients had a follow-up period of at least 18 months, and none of the patients were lost to follow-up. We obtained all

Table II. Comparison of the main clinical features of anti-NXP2 positive patients with and without ILD.

Features	NXP2 with ILD (n=14)	NXP2 without ILD (n=19)	p-value
Gender, M/F	11/3	13/6	0.698
Age at onset (years), median (IQR)	53 (44.8, 60)	31 (17, 46)	**0.002**
Age (years), median (IQR)]	53.5 (45, 60)	31 (19, 49)	**0.002**
Duration (months), median (IQR)	3 (1, 6.8)	3 (1, 24)	0.604
FVC (%), median (IQR)	72.9 (62.5, 85.3)	100 (96, 107)	**<0.001**
DLco (%), median (IQR)	61.5 (45.5, 77.5)	88 (84, 94)	**<0.001**
Dysphagia, n (%)	8 (57.1)	9 (47.4)	0.728
Choking, n (%)	6 (42.9)	6 (31.6)	0.716
Tobacco smoking, n (%)	2 (14.3)	4 (21.1)	1.0
Malignancy, n (%)	0	2 (10.5)	0.496
Overlap MSAs, n (%)	3 (21.4)	0	0.067
CK peak (IU/L), median (IQR)]	2654 (905, 8325)	2663 (700, 5099)	0.636
SF (ng/ml), median (IQR)	594 (302, 1419)	335 (78, 727)	0.105
LDH (IU/L), median (IQR)	521 (336, 658)	345 (291, 693)	0.334
CRP (mg/L), median (IQR)	6.4 (1.8, 26.3)	2 (1, 4.5)	**0.036**
ESR (mm/H), median (IQR)	27 (10, 62)	15 (9, 28)	0.15
Anti-Ro52 antibody positive, n (%)	8 (57.1)	6 (31.6)	0.173

NXP2: nuclear matrix protein 2; ILD: interstitial lung disease; FVC: forced vital capacity; Dlco: diffusing capacity for carbon monoxide; MSAs: myositis-specific autoantibodies; CK: creatinine kinase; SF: serum ferritin; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

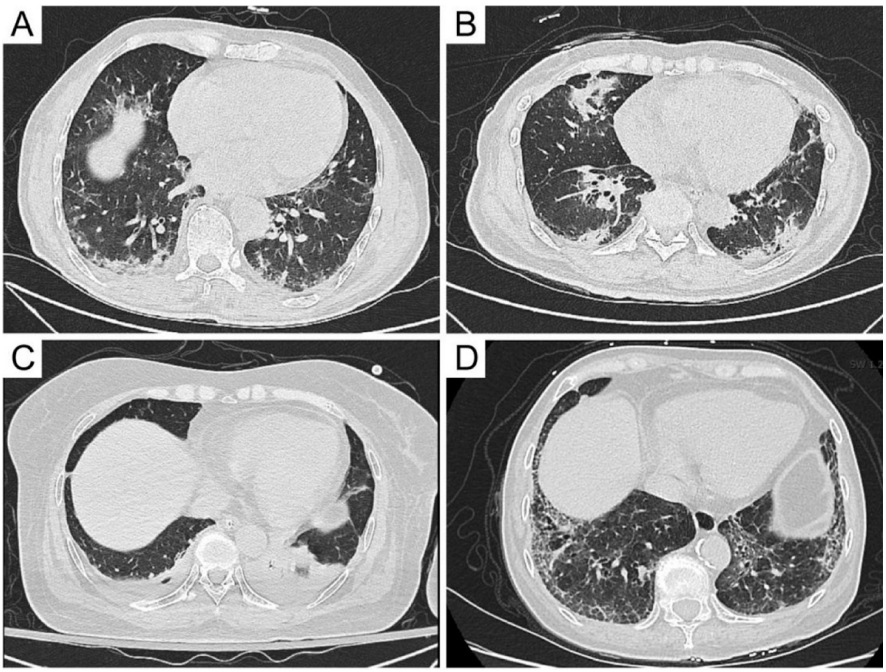

Fig. 1. Various types of HRCT patterns and images.
A: NSIP+OP pattern; **B**-**C**: OP pattern; **D**: NSIP+probable UIP.

Table III. Various manifestations of pulmonary lesions in anti-NXP2 positive patients with and without ILD.

Features	NXP2 with ILD (n=14)	NXP2 without ILD (n=19)
Respiratory symptoms at onset, n	3	0
Dyspnea, n	1	1
Mechanical ventilation, n	0	1
Pleural effusion, n	1	1
DAH, n	0	1
Lung cancer, n	0	1
ILD patterns, n		
NSIP, n	6	...
OP+NSIP, n	3	...
OP, n	2	...
Probable UIP+NSIP, n	1	...
Probable UIP+OP, n	1	...
Indeterminate, n	1	...
Bacterial infection, n	1	3
Fungal infection, n	1	1

DAH: diffuse alveolar haemorrhage; ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; UIP: usual interstitial pneumonia.

Table IV. Univariate and multivariate analysis of the influence of clinical variables in anti-NXP2 positive patients with ILD.

	Univariate logistic analysis			Multivariate logistic analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Anti-NXP2 antibody titre	0.518	0.207-1.297	0.16	...	...	...
Duration	0.943	0.858-1.036	0.218	...	...	...
Gender	1.692	0.341-8.396	0.52	...	...	...
Age	1.094	1.023-1.171	**0.009**	1.119	1.029-1.216	**0.008**
Dysphagia	0.675	0.168-2.709	0.579	...	...	...
Tobacco smoking	1.6	0.249-10.272	0.62	...	...	...
CRP	1.043	0.98-1.109	0.183	...	...	...
LDH	1.001	0.998-1.004	0.356	...	...	...
SF	1.001	1.0-1.002	0.165	...	...	...
Anti-Ro52 antibody positive	0.346	0.083-1.452	0.147	...	...	...
Anti-Ro52 antibody titre	1.354	0.776-2.363	0.285	...	...	...

NXP2; nuclear matrix protein 2; CRP: C-reactive protein; ILD: lactate dehydrogenase; SF: serum ferritin.

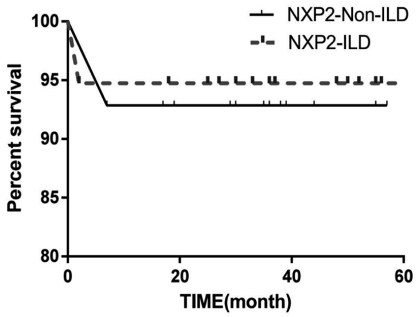

Fig. 2. Long-term survival curves were calculated using Kaplan-Meier survival curves.

survival information during the last date of follow-up. The median follow-up duration for surviving patients was 27 months (range: 18–54 months). The median survival time from disease onset to death or the last follow-up was 30 months (range: 2–258 months), and 31 patients (93.9%) were still alive at the time of the last follow-up. A total of 2 patients (6.1%) died in this cohort, and one additional patient had pneumonia and suspected aspiration that improved after treatment with antibiotics. Kaplan-Meier survival curves displayed no association between ILD and all-cause death (log-rank p=0.84), (Fig. 2). Among the two patients who died, 1 patient succumbed to lung infection, and 1 patient succumbed to rhabdomyolysis with the combination of extensive subcutaneous oedema, diffuse gastrointestinal bleeding and DAH. There were no deaths from progressive fibrosis.

Discussion

DM is an ancient and complex group of diseases. Recent years have witnessed remarkable strides in our understanding of MSAs, which may ultimately improve the diagnosis and subclassification of dermatomyositis patients (16-18). Anti-NXP2 antibodies are also associated with a unique clinical subset of DM, making them useful in predicting and monitoring certain clinical manifestations. A systematic review and meta-analysis showed that anti-NXP2 antibody was negatively associated with ILD (OR=0.26) (8). However, this is not all the evidence. There was a considerable amount of ILD-susceptible antibodies (*e.g.* anti-MDA5 antibody or anti-synthase antibody) in the control group, which led to an underestimation of the absolute description of the incidence of ILD in anti-NXP2-positive DM patients. Yang *et al*. showed in an analysis of 56 patients with positive anti-NXP2 antibodies that ILD was reported in 26.8% (n=15) of cases (5), although there was little information focused on describing ILD. Inour previous study, we reported that the prevalence was 35.3% (6/17) in ILD cases (19), but it still shows low risk in comparative data. This is an unexpected result. However, the evidence is far from enough. More comprehensive real data on the association of ILD and anti-NXP2 antibody positivity need to be obtained to further our understanding of its patterning. This was also the original intention of this study.

Anti-NXP2 antibody was first described in 1997 by Oddis in juvenile DM (20) and has a prominent age-related susceptibility (meta-analysis: OR= 62.48, 95% CI: 16.97–229.98, p<0.001) (8). In an Argentine Caucasian cohort (21), anti-NXP2 antibodies were the most prevalent antibodies in JM (up to 28.1%). Upon literature review, there were some small differences between adult IIMs and JMs in their association with other clinical presentations; for example, children may be more likely to suffer from calcinosis (22). However, the differences in lung involvement between adults and children are still unknown. Our data showed apparent age difference between anti-NXP2-positive DM patients with ILD and those without ILD. This translates to an increase in susceptibility with increasing age based

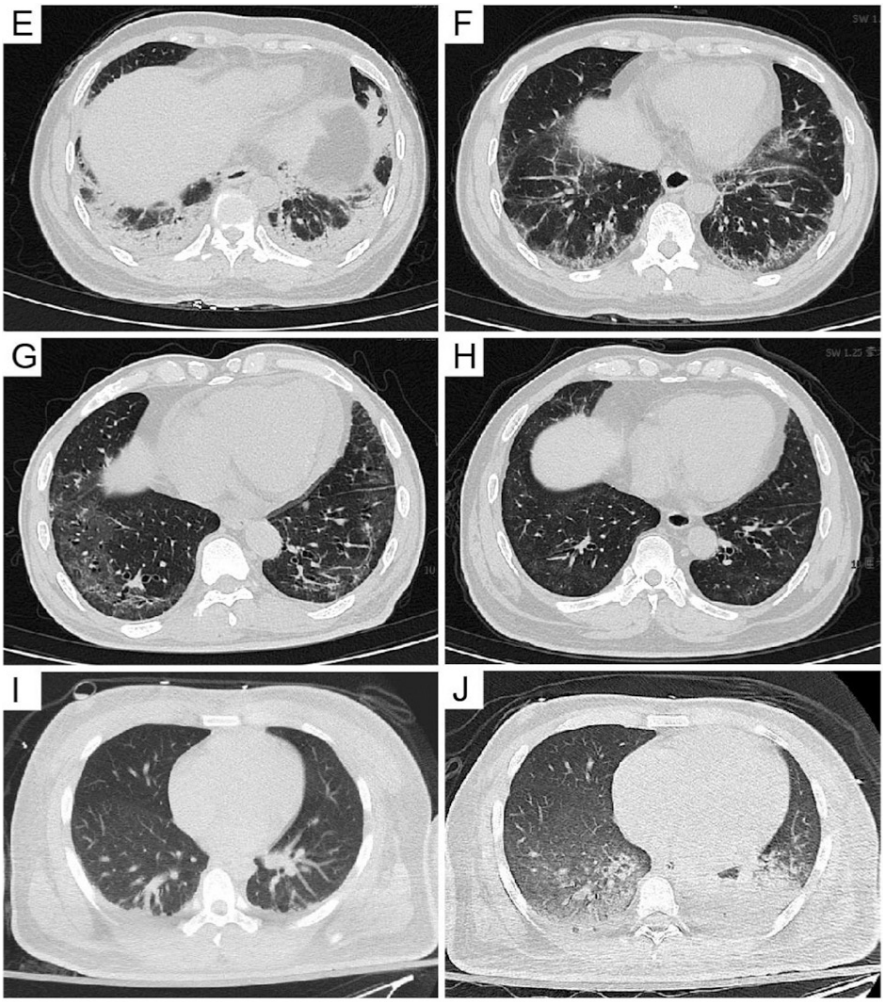

Fig. 3. Imaging outcomes of treatment in some cases.
E-**F**: A patient with early lung consolidation developed a background residual fibrosis of possible UIP after treatment.
G-**H**: The other patient's lung image improved significantly after treatment.
I-**J**: Pulmonary changes in a fatal case, he rapidly deteriorated to diffuse alveolar haemorrhage until death.

on the results of the logistic regression analysis model. We searched the literature for other evidence to support our predictions. Sabbagh *et al*. (23) reported a large sample cohort of children, in which ILD occurred in only 1 out of 77 cases with anti-NXP2 positivity, with a frequency of less than 1.3%. The study by Yang *et al*. included 83.9% adults, and 15 of 56 patients (26.8%) positive for anti-NXP2 antibody had ILD (5). This difference may be because our study focused exclusively on adult cases, resulting in an incidence as high as 42.4%. Of course, this speculation needs further investigation.

We highlight HRCT screening for all hospitalisations at baseline and describe the HRCT patterns (Table III). We also found some other interesting cases. An anti-NXP2-positive patient with ILD was eventually diagnosed with IPAF (24), and this patient lacked other clinical manifestations of rash and muscle damage. In one case, we also found early lung consolidation and later found background residual fibrosis of probable UIP (Fig. 3 E-F), Another patient received glucocorticoid and cyclophosphamide and had an excellent radiographic outcome (Fig. 3 G-H). These may be an imaging change in disease course outcome. In addition to ILD, we found other indications of lung involvement. In non-ILD patients who had only a small bilateral pleural effusion in the early stages and rapidly deteriorated to DAH, rhabdomyolysis, and diffuse gastrointestinal bleeding, which led to patient death (Fig. 3 I-J). Due to the lack of HRCT controls for all patients, we could not draw meaningful statistical conclusions.

We focused on ILD not only because of the high incidence in IIMs but also because of the high mortality (25-27). We observed mild outcomes in patients who were anti-NXP2 positive. This is in line with the conclusions of earlier studies; nevertheless, our study has provided more long-term evidence at the 18-month follow-up.

It is worth noting that MSAs are generally mutually exclusive (28). However, the detection of MSA coexistence is also not rare. We did not exclude three cases of coexisting antibodies, which partially overlapped with the anti-MDA5, anti-EJ, and anti-SRP antibodies. We argue that the cohort of patients with independent anti-NXP2 antibodies has been extensively studied and that overlap exists in the real world and should still be taken into account when interpreting results. We know that the susceptibility of various types of MSAs to ILD is different, depending on the type of overlapping antibody. We also believe that 3 cases of coexisting antibodies had a significant effect on ILD, although this is not entirely clear. To date, there is no evidence to show that coexisting antibodies eventually lead to responsible antibodies or act together.

This is the largest case-control study to date describing ILD associated with anti-NXP2 antibodies. However, there are several limitations to this current study. First, cohort does not include patients at dermatology centres or outpatient clinics, which may have caused selection bias towards severely ill patients. Therefore, we do not overemphasise the ILD incidence of the disease but offer some explanations and supplementary comments for our conclusions. Second, there are many ways to recognise these MSAs (29-30). However, no other laboratory tests were used to verify the anti-NXP2 antibody in our study. Third, the classification of ILD depends only on HRCT, not pathological biopsy. Fourth, we did not report the treatments because it was up to the individual opinions of rheumatologists, which made it too difficult to find meaningful statistical differences.

In this study, we concluded that adult patients who were positive for anti-NXP2 antibodies mainly had dermatomyositis, and IPAF was also present. Concurrent ILD is not uncommon, but clinical manifestations are often latent. We reported various types of HRCT patterns and images, confirming that age has an important influence on ILD occurrence and suggesting that older adults are susceptible. Finally, our study provided long-term evidence of 18 months, and the survival analysis results did not support the effect of ILD progression on their death. It is hoped that these data and our summary will help in making earlier and more accurate diagnoses for ILD in patients with anti-NXP2 antibody positivity and will aid in the better management of these patients in clinical practice in the future.

References

1. DEWANE ME, WALDMAN R, LU J: Dermatomyositis: Clinical features and pathogenesis. *J Am Acad Dermatol* 2020; 82: 267-81. https://doi.org/10.1016/j.jaad.2019.06.1309
2. 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. *JAMA Neurol* 2018; 75: 1528-37. https://doi.org/10.1001/jamaneurol.2018.2598
3. BOLKO L, GITIAUX C, ALLENBACH Y: Dermatomyositis: new antibody, new classification. *Med Sci* (Paris) 2019; 35: 18-23. https://doi.org/10.1051/medsci/2019178
4. TAKEUCHI E, HIROZAWA D, OKIYAMA N *et al*.: A case of dermatomyositis positive for anti-nuclear matrix protein 2 antibody without dermatologic symptoms. *Rinsho Shinkeigaku* 2021; 61: 258-61. https://doi.org/10.5692/clinicalneurol.cn-001528
5. YANG H, LU X, PENG Q *et al*.: Differential clinical associations of anti-nuclear matrix protein 2 autoantibodies in patients with idiopathic inflammatory myopathies. *Arthritis Rheumatol* 2018; 70: 1288-97. https://doi.org/10.1002/art.40491
6. ALBAYDA J, PINAL-FERNANDEZ I, HUANG W *et al*.: Dermatomyositis patients with anti-nuclear matrix protein-2 autoantibodies have more edema, more severe muscle disease, and increased malignancy risk. *Arthritis Care Res* 2017; 69: 1771-6. https://doi.org/10.1002%2Facr.23188
7. CERIBELLI A, FREDI M, TARABORELLI M *et al*.: Anti-MJ/NXP-2 autoantibody specificity in a cohort of adult Italian patients with polymyositis/dermatomyositis. *Arthritis Res Ther* 2012; 14: R97. https://doi.org/10.1186/ar3822
8. LI L, LIU C, CHENG L *et al*.: Assessment of diagnostic utility, clinical phenotypic associations, and prognostic significance of anti-NXP2 autoantibody in patients with idiopathic inflammatory myopathies: a systematic review and meta-analysis. *Clin Rheumatol* 2021; 40: 819-32. https://doi.org/10.1007/s10067-020-05291-1
9. BERMUDEZ J, HEIM X, BERTIN D *et al*.: Lung involvement associated with anti-NXP2 autoantibodies in inflammatory myopathies: a French monocenter series. *Expert Rev Respir Med* 2020; 14: 845-50. https://doi.org/10.1080/17476348.2020.1767598
10. GOSSEZ M, LEVESQUE M, KHOUATRA C *et al*.: Interstitial lung disease in an adult patient with dermatomyositis and anti-NXP2 autoantibody. *Eur Respir Rev* 2015; 24: 370-2. https://doi.org/10.1183/16000617.00006714
11. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-7. https://doi.org/10.1056/nejm197502132920706
12. AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277-304. https://doi.org/10.1164/ajrccm.165.2.ats01
13. SPRUIT MA, SINGH SJ, GARVEY C *et al*.: An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; 188: e13-64. https://doi.org/10.1164/rccm.201309-1634st
14. WU W, GUO L, FU Y *et al*.: Interstitial lung disease in anti-MDA5 positive dermatomyositis. *Clin Rev Allergy Immunol* 2021; 60: 293-304. https://doi.org/10.1007/s12016-020-08822-5
15. GONO T, MASUI K, NISHINA N *et al*.: Risk prediction modeling based on a combination of initial serum biomarker levels in polymyositis /dermatomyositis-associated interstitial lung disease. *Arthritis Rheumatol* 2021; 73: 677-86. https://doi.org/10.1002/art.41566
16. 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. *JAMA Neurol* 2018; 75: 1528-37. https://doi.org/10.1001/jamaneurol.2018.2598
17. TANBOON J, URUHA A, STENZEL W *et al*.: Where are we moving in the classification of idiopathic inflammatory myopathies? *Curr Opin Neurol* 2020; 33: 590-603. https://doi.org/10.1097/wco.0000000000000855
18. CARDELLI C, ZANFRAMUNDO G, COMETI L *et al*.: Idiopathic inflammatory myopathies: one year in review 2021. *Clin Exp Rheumatol* 2022; 40: 199-209. https://doi.org/10.55563/clinexprheumatol/vskjxi
19. YAN TT, ZHANG X, YANG HH *et al*.: Association of anti-NXP2 antibody with clinical characteristics and outcomes in adult dermatomyositis: results from clinical applications based on a myositis-specific antibody. *Clin Rheumatol* 2021; 40: 3695-702. https://doi.org/10.1007/s10067-021-05667-x
20. ODDIS CV, FERTIG N, GOEL A *et al*.: Clinical and serological characterization of the anti-MJ antibody in childhood myositis. *Arthritis Rheum* 1997; 40: S139.
21. ESPADA G, MALDONADO COCCO JA *et al*.: Clinical and serologic characterization of an Argentine pediatric myositis cohort: identification of a novel autoantibody (anti-MJ) to a 142-kDa protein. *J Rheumatol* 2009; 36: 2547-51. https://doi.org/10.3899/jrheum.090461
22. TANSLEY SL, BETTERIDGE ZE, SHADDICK G *et al*.: Juvenile Dermatomyositis Research Group. Calcinosis in juvenile dermatomyositis is influenced by both anti-NXP2 autoantibody status and age at disease onset. *Rheumatology* (Oxford) 2014; 53: 2204-8. https://doi.org/10.1093/rheumatology/keu259
23. SABBAGH S, PINAL-FERNANDEZ I, KISHI T *et al*.: Anti-Ro52 autoantibodies are associated with interstitial lung disease and more severe disease in patients with juvenile myositis. *Ann Rheum Dis* 2019; 78: 988-95. https://doi.org/10.1136/annrheumdis-2018-215004
24. FISCHER A, ANTONIOU KM, BROWN KK *et al*.: An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J* 2015; 46: 976-87. https://doi.org/10.1183/13993003.00150-2015
25. HALLOWELL RW, PAIK JJ: Myositis-associated interstitial lung disease: a comprehensive approach to diagnosis and management. *Clin Exp Rheumatol* 2022; 40: 373-83. https://doi.org/10.55563/clinexprheumatol/brvl1v
26. BRITO Y, GLASSBERG MK, ASCHERMAN DP: Rheumatoid arthritis-associated interstitial lung disease: current concepts. *Curr Rheumatol Rep* 2017; 19: 79. https://doi.org/10.1007/s11926-017-0701-5
27. LIAN X, ZOU J, GUO Q *et al*.: Mortality risk prediction in amyopathic dermatomyositis associated with interstitial lung disease: the FLAIR model. *Chest* 2020; 158: 1535-45. https://doi.org/10.1016/j.chest.2020.04.057
28. RIDDELL V, BAGBY S, MCHUGH N: Myositis autoantibodies: recent perspectives. *Curr Opin Rheumatol* 2020; 32: 548-52. https://doi.org/10.1097/bor.0000000000000742
29. CASAL-DOMINGUEZ M, PINAL-FERNANDEZ I, PAK K *et al*.: The indirect immunofluorescence assay autoantibody profiles of myositis patients without known myositis-specific autoantibodies. *Clin Exp Rheumatol* 2021; 39: 519-24. https://doi.org/10.55563/clinexprheumatol/7kyr5e
30. PIETTE Y, DE SLOOVERE M, VANDENDRIESSCHE S *et al*.: Pitfalls in the detection of myositis specific antibodies by lineblot in clinically suspected idiopathic inflammatory myopathy. *Clin Exp Rheumatol* 2020; 38: 212-19. https://doi.org/10.55563/clinexprheumatol/3cuc1s