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Anti-Ku antibody-positive interstitial lung disease: A retrospective study of 13 patients

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Abstract

Background

Although anti-Ku antibodies have been reported in various connective tissue diseases (CTDs), data on the clinical characteristics of anti-Ku antibody-positive interstitial lung disease (ILD) remains limited. This study investigated the clinical, radiological, and pathological features of anti-Ku antibody-positive ILD.

Methods

We retrospectively reviewed 13 patients with anti-Ku antibody-positive ILD at our institution between 2018 and 2025. Data on baseline characteristics, imaging, pathology, treatment, and outcomes were collected.

Results

Seven patients were diagnosed with CTDs. CTD was present in idiopathic inflammatory myopathy (IIM; n = 2), Systemic sclerosis (SSc), IIM with SSc overlap, microscopic polyangiitis, rheumatoid arthritis, and Sjögren's syndrome (n = 1, each). ILD preceded the diagnosis of CTDs in two of these patients. Nonspecific interstitial pneumonia (NSIP) was the most frequent pattern (n = 5, 38.5%) on chest computed tomography, followed by usual interstitial pneumonia (UIP, n = 4, 30.8%). On lung histopathology, NSIP with organizing pneumonia was the most frequent pathological pattern (n = 3, 37.5%), whereas UIP features were present in four patients. During the observation period (51.7 ± 32.1 months), four patients developed progressive pulmonary fibrosis (PPF). Among the seven patients in whom any radiological or pathological UIP feature was present, four (57.1%) developed PPF or experienced acute exacerbation.

Conclusions

Anti-Ku antibody-positive ILD can exhibit progressive fibrotic behavior regardless of the CTD diagnosis. Radiological and/or pathological UIP features might represent indicators of disease progression. Careful follow-up is encouraged to ensure the early detection of CTD and fibrotic progression.

1. Background

Interstitial lung disease (ILD) is a major organ manifestation of connective tissue diseases (CTDs) that has a substantial impact on morbidity and mortality [1]. Although the prevalence of ILD differs among diseases, it has been reported in all CTDs. ILD is common in idiopathic inflammatory myopathy (IIM), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD). Additionally, ILD is frequently observed in rheumatoid arthritis (RA) and Sjögren's syndrome (SjS), whereas it is relatively rare in systemic lupus erythematosus (SLE) [2].

Anti-Ku antibodies are directed against the Ku antigen, a heterodimeric DNA-binding protein composed of 70- and 80-kDa subunits that plays essential roles in the repair of DNA double-strand breaks and maintenance of telomere length [3]. Anti-Ku antibodies were first identified by Mimori et al. in 1981 in patients with overlap syndromes involving polymyositis and SSc [4]. These antibodies are most frequently detected in IIM and SSc; however, they can be present in other autoimmune diseases, including SSc, SLE, and MCTD [5].

Among autoantibody-associated ILDs, anti–aminoacyl-tRNA synthetase antibody-positive ILD has been most extensively studied [6]. Conversely, reports comprehensively describing anti-Ku antibody-positive ILD are scarce [7]. Hence, this study aimed to characterize anti-Ku antibody-positive ILD in terms of its clinical, radiological, functional, and pathological features.

2. Patients and methods

2.1. Study design and setting

This retrospective, observational study included patients who were managed at our institution between 2018 and 2025.

2.2. Eligibility criteria

The study included patients who had a positive anti-Ku antibody test result and evidence of ILD on chest computed tomography. Autoantibody testing was performed using an immunoblot assay (EUROLINE, Myositis Profile 3; EUROIMMUN AG, Lübeck, Germany). Borderline ("±") results were excluded, and a reactivity value of ≥ 1 + was considered positive.

2.3. Diagnostic criteria

CTDs were diagnosed using established international classification criteria for each specific condition [1–7]. Idiopathic interstitial pneumonias (IIPs) were diagnosed through multidisciplinary discussions that integrated clinical, radiological, and pathological findings. Progressive pulmonary fibrosis (PPF) was defined in accordance with the 2022 ATS/ERS/JRS/ALAT guidelines [8].

2.4. Collected data

We collected the following data from patients' medical records: clinical data including age, sex, smoking history, symptoms, and final diagnoses; laboratory findings including autoantibodies and serologic markers; radiological and pathological findings; administered treatments; and outcomes.

High-resolution computed tomography (HRCT) scans were reviewed by two pulmonologists. The radiological patterns and distribution of lung lesions as well as the extent of fibrosis were evaluated according to international guidelines [9]. Lung biopsy specimens were reviewed by two pathologists. Histological patterns were classified according to the International Multidisciplinary Classification of Idiopathic Interstitial Pneumonias. Among unclassifiable patterns, NSIP with organizing pneumonia (NSIP + OP) was categorized separately [10].

Pulmonary function tests, including percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity of the lung for carbon monoxide ($\%DL_{CO}$), were performed at diagnosis and repeated during follow-up, whenever possible. Additionally, Information on treatment with glucocorticoids and immunosuppressive agents was also collected. The follow-up period was defined as the interval from the first visit to our institution to the last clinical assessment or death.

2.5. Statistical analysis

Due to the small sample size, statistical analyses were mainly descriptive. Continuous variables are presented as mean ± standard deviation or median with range, depending on the data distribution, whereas categorical variables are shown as counts and percentages. Group comparisons, such as those between patients with and without radiological or pathological UIP features, were exploratory and did not involve formal hypothesis testing. Therefore, *p*-values were not used to draw definitive conclusions. All statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

3. Results

3.1. Patient characteristics

The clinical characteristics of the 13 patients are summarized in Table 1, and their baseline demographics are presented in Table 2. The cohort consisted of seven men and six women with a mean age of 63.9 ± 13.9 years (range, 32–85). The observation period ranged from 24 to 144 months (mean, 51.7 ± 32.1 months). The mean age at ILD diagnosis was 59.0 ± 14.7 years (range, 32–84). The interval between CTD and ILD diagnoses ranged from − 2 (preceded the development of ILD by two years) to 14 years. ILD preceded CTDs in two patients, whose underlying diseases were MPA and IIM, respectively. The intervals from ILD onset to CTD diagnosis in these two patients were 12 and 24 months, respectively. Overall, four patients (30.8%) were ever-smokers, and the prevalence of smoking tended to be lower in patients with CTDs than in those with IIPs.

Table 1
Patient characteristics at the diagnosis of ILD associated with anti-Ku antibody

Case	Sex	Age	Smoking history (B.I)	Respiratory symptoms	Clinical features	CTD diagnosis	FVC, %	DLco, %	CT patterns	Honey combing	Pathological patterns	FF	Fo up
1	F	65	-	SOB, dry cough	Sclerodactyly, Raynaud's phenomenon	SSc	62.8	38	Probable UIP	-	Unclassifiable (NSIP + UIP)	+	84
2	F	45	-	Dry cough	Sclerodactyly, Raynaud's phenomenon	IIM/SSc	93.3	71.6	NSIP	-	N/A		14
3	M	73	240	Dry cough	Arthralgia	MPA	66.6	57.8	Unclassifiable (UIP + NSIP + OP)	-	UIP	+	60
4	F	72	-	-	Arthralgia, Muscle weakness	IIM	78.8	74.9	Probable UIP	-	N/A		60
5	F	78	-	SOB, dry cough	-	-	50.2	N/A	NSIP	-	N/A		36
6	M	74	740	SOB, dry cough	-	-	72	49.7	Unclassifiable (NSIP + UIP)	+	Unclassifiable (NSIP + OP + UIP)	+	24
7	F	32	-	SOB	Arthralgia, Sicca syndrome, Gastroesopha-geal reflux	-	72.4	31.5	NSIP	-	NSIP + OP	-	48
8	M	85	200	SOB	-	-	73.7	112.4	Probable UIP	-	N/A		48
9	M	55	-	SOB, dry cough	Periungual erythema	-	112.4	61.33	NSIP + OP	-	NSIP + OP	-	36
10	F	56	-	-	-	SjS	88.8	76.1	NSIP	-	Unclassifiable (NSIP + OP + UIP)	-	24
11	M	57	-	-	Arthralgia, Myalgia	IIM	70.2	N/A	Probable UIP	-	N/A		24
12	M	70	900	-	Arthralgia, Sicca syndrome, Sclerodactyly	RA	87.6	69.4	NSIP	-	fNSIP	-	24
13	M	69	-	SOB, dry cough	Arthralgia, Mechanic's hand	-	37.2	N/A	NSIP + OP	-	NSIP + OP	-	60

M, male; F, female; B.I, brinkman index; SOB, shortness of breath; CTD, connective tissue disease; SSc, systemic sclerosis; IIM: idiopathic inflammatory myop SjS, Sjögren's syndrome; RA, rheumatoid arthritis; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia; FF, fil exacerbation; PPF, Progressive Pulmonary Fibrosis; PH, pulmonary hypertension

Table 2
Patient characteristics of ILD associated with anti-Ku antibody (n = 13)

Variable	Value
Male/Female	7 (53.8)/6 (46.2)
Age (years)[a]	63.9 ± 13.9(32–85)
Acute onset/subacute onset/chronic onset	0 (0)/2 (15.4)/11 (84.6)
Smoking status (current/past/never)	0 (0)/4 (30.8)/9 (69.2)
Follow-up period (months)[a]	51.7 ± 32.1 (24–144)
Immunosuppresive therapy/Antifibrotic therapy/no medication	12 (92.3)/3 (23.1)/0
Diagnosis as CTD (n = 7)	
IIM	2 (28.6)
SSc	1 (14.3)
IIM/SSc overlap	1 (14.3)
RA	1 (14.3)
SjS	1 (14.4)
MPA	1 (14.5)
Laboratory findings	
CK (IU/L)[a]	278.7 (29–1549)
CRP (mg/dL)[a]	1.86 (0.10–12.74)
KL-6 (U/mL)[a]	1507 (452–7724)
SP-D (ng/mL)[a]	300 (63.4–773.0)
PFT results	
FVC(L)	2.21 ± 0.71
FVC, % predicted	74.3 ± 18.4
FEV1.0	1.88 ± 0.50
FEV1.0, % predicted	83.8 ± 18.1
DLco, % predicted	64.3 ± 21.6
BAL findings[b]	
Neutrophils (%)	2 (25.0)
Lymphocytes (%)	5 (62.5)
Macrophages (%)	1 (12.5)
Eosinophils (%)	0
Clinical features (%)	
Arthralgia	6 (46.2)
Sclerodactyly	3 (23.1)
Raynaud's phenomenon	2 (15.4)
Sicca syndrome	2 (15.4)
Muscle weakness	1 (7.7)
Myalgia	1 (7.7)
Mechanic's hand	1 (7.7)
Gastroesophageal reflux	1 (7.7)
periungual erythema	1 (7.7)

[b] Data were available for 15 patients

Variable	Value
Except where otherwise indicated, data are presented as no. (%) of patients.	
CTD, connective tissue disease; SSc, systemic sclerosis; IIM, idiopathic inflammatory myopathy; MPA, microscopic polyangiitis; SjS, Sjögren's syndrome; RA, rheumatoid arthritis; CK, creatine kinase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; PFT, pulmonary function test; FVC, forced vital capacity; DL_{CO}, diffusing capacity of the lung for carbon monoxide; BAL, bronchoalveolar lavage	
[a] Median (range)	
[b] Data were available for 15 patients	

CTDs were detected in seven patients (53.8%). The most frequent CTD was IIM (n = 2, 28.6%), followed by SSc (n = 1, 14.3%), IIM with SSc overlap (n = 1, 14.3%), SjS (n = 1, 14.3%), RA (n = 1, 14.3%), and MPA (n = 1, 14.3%).

Regarding clinical manifestations, arthralgia was the most common symptom (n = 6, 46.2%), followed by sclerodactyly (n = 3, 23.1%), Raynaud's phenomenon (n = 2, 15.4%), and sicca symptoms (n = 2, 15.4%). Muscle weakness, myalgia, mechanic's hands, gastroesophageal reflux, and periungual erythema, each of which was observed in one patient (7.7%). The mean creatine kinase level at baseline was 278.7 IU/L (range, 29–1,549); CK was above the upper limit of normal in three patients (case 2, 4, 12).

Among autoantibodies other than anti-Ku, antinuclear antibodies were most frequently detected (n = 10, 76.9%). Speckled and homogeneous patterns were observed in nine and seven patients, respectively, and one patient exhibited a nucleolar pattern. Rheumatoid factor was positive in four patients (30.7%). Anti–double-stranded DNA antibodies were positive in one patient, who did not have concomitant chronic kidney disease. Isolated anti-Ku antibody positivity, without other myositis-specific or CTD-related autoantibodies, was found in seven patients.

Concerning pulmonary function at baseline, mean %FVC was 74.3% ± 18.4%, the mean total lung capacity was 76.1% ± 17.0% of predicted, and mean $\%DL_{CO}$ was 64.3% ± 21.6%. Nine patients (69.2%) exhibited a restrictive ventilatory defect, and $\%DL_{CO}$ was < 70% in seven patients (53.8%). The mean annual change in FVC was + 88 ± 27 mL/year (range, − 22 to + 650), and the mean annual change in $\%DL_{CO}$ was − 3.89%/year ± 9.07%/year (range, − 28.8 to 14.6). The longitudinal changes in pulmonary function in each patient are presented in Fig. 1. Four patients (30.8%) met the criteria for PPF during follow-up.

3.2. Radiological and pathological findings

Radiological features on HRCT are summarized in Table 3, and representative images for each patient are presented in Fig. 2. Reticulation was the most frequent finding (n = 12, 92.3%), followed by ground-glass opacities (GGOs) in nine patients (69.2%). Traction bronchioloectasis was observed in six patients (46.2%). Honeycombing was present in one patient (7.7%). The most common radiological pattern was NSIP (n = 5, 38.5%), followed by NSIP + OP (n = 2, 15.4%). An usual interstitial pneumonia (UIP) pattern was noted in four patients (30.8%). The distribution of lesions was predominantly basal (n = 11, 84.6%).

Table 3
Radiological analysis of ILD associated with anti-Ku antibody (n = 13)

Variable	Value
Radiological diagnosis	
NSIP	5 (38.5)
OP	0
UIP	4 (30.8)
NSIP + OP	2 (15.4)
Unclassifiable	2 (15.4)
HRCT findings	
Ground-glass opacity	9 (69.2)
Consolidation	4 (30.8)
Reticulation	12 (92.3)
Traction bronchioloectasis	6 (46.2)
Honeycombing	1 (7.70)
Cyst	5 (38.5)
Emphysema	1 (7.70)
Micronodules	1 (7.70)
Mediastinal lymphadenopathy	4 (30.8)
All data are presented as no. (%) of patients.	
NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography	

Pathological findings are summarized in Table 4, and representative histological images are presented in Fig. 3. Surgical lung biopsy was performed in one patient via video-assisted thoracic surgery, and transbronchial lung cryobiopsy was utilized in seven patients. The pathological patterns included fibrotic NSIP in one patient, NSIP + OP in three patients, and UIP in one patient. An unclassifiable pattern was observed in three patients, including two patients with NSIP + OP + UIP features and one with NSIP + UIP features. Radiological and pathological findings were fully concordant in three patients (cases 9, 12, and 13), whereas partial concordance was observed in four patients (cases 1, 3, 6, and 7). In one other patient (case 10), pathological examination revealed UIP features that were not detected on HRCT.

Table 4
Pathological findings of ILD associated with anti-Ku antibody (n = 8)

Variable	Values
Pathological diagnosis	
UIP	1 (12.5)
fNSIP	1 (12.5)
NSIP + OP	3 (37.5)
Unclassifiable (NSIP + OP + UIP)	2 (25.0)
Unclassifiable (NSIP + UIP)	1 (12.5)
All data are presented as no. (%) of patients.	
Of the 13 patients in this study, one underwent surgical lung biopsy (SLB), and seven underwent transbronchial lung cryobiopsy (TBLC) for a diagnosis of ILD.	
NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia	

3.3. Treatment and outcomes

During follow-up, patients received glucocorticoids (n = 12, 92.3%), tacrolimus (n = 9), mycophenolate mofetil (n = 3), azathioprine (n = 2), cyclophosphamide (n = 1), cyclosporine (n = 1), abatacept (n = 1), methotrexate (n = 1), pirfenidone (n = 1) and nintedanib (n = 3). Overall, 12 patients (92.3%) received anti-inflammatory treatment, and antifibrotic agents were administered in three patients (23.1%). One patient initially received pirfenidone, which was later switched to nintedanib, and the remaining two patients were treated with nintedanib as first-line antifibrotic therapy. In one patient, antifibrotic therapy was given without concomitant anti-inflammatory treatment. All 12 patients who received anti-inflammatory therapy were treated with glucocorticoids, including glucocorticoid monotherapy in one patient and additional immunosuppressive agents in the remaining patients. Tacrolimus was the most frequently used

immunosuppressant (n = 9, 75%). In one patient with polymyositis, glucocorticoids were successfully discontinued, and disease control was maintained with tacrolimus and abatacept.

During follow-up, five patients (38.5%) died. The mean interval from diagnosis to death was 50.4 ± 23.1 months. Causes of death included acute exacerbation of ILD, aspiration pneumonia, worsening heart failure, and chronic respiratory failure. The cause of death was unknown in one patient.

4. Discussion

This retrospective study described a case series of 13 patients with anti-Ku antibody-positive ILD. Although individual case reports have been published, Laure et al. reported the first series of 19 patients with anti-Ku antibody-positive ILD [7]. To our knowledge, this is the first case series from Japan to comprehensively evaluate the onset patterns, clinical features, radiological findings, and pathological findings of anti-Ku antibody-positive ILD.

In agreement with the findings of Laure et al., most of our patients (n = 11, 84.6%) exhibited a chronic disease onset. In contrast to previous reports on anti-Ku antibody-positive ILD, ILD preceded the diagnosis of CTD in two patients, whose underlying diseases were MPA and IIM, respectively. Notably, ILD is known to precede systemic manifestations in both MPA and IIM [11–13]. Our findings suggest that ILD-preceding disease can also occur in anti-Ku antibody-positive ILD, and careful long-term follow-up is required to detect subsequent development of CTD.

Regarding clinical manifestations, we observed frequent findings related to IIM and SSc, such as arthralgia and sclerodactyly, consistent with prior reports [7]. Contrarily, four patients in our cohort had few systemic physical findings, and three of them did not meet the classification criteria for CTDs during the observation period. These patients were older, predominantly male, and more likely to be smokers. They presented with clinical backgrounds suggestive of IIPs, particularly idiopathic pulmonary fibrosis (IPF). Anti-Ku antibodies have been reported mainly in overlap syndromes involving IIM and SSc [7], but our series demonstrated that they might also be present in patients with minimal or no CTD manifestations. Thus, anti-Ku antibody positivity does not necessarily indicate a typical CTD-associated ILD phenotype, and a subset of anti-Ku antibody-positive cases might be “lung-dominant” with an IPF-like IIP phenotype. This highlights the difficulty of simply considering anti-Ku antibodies as markers of CTDs and underscores the need for further accumulation of cases and immunologic studies.

In current case series, the radiological and pathological findings were heterogeneous. On HRCT, NSIP and NSIP + OP were the most frequent patterns, consistent with previous reports [7], whereas UIP patterns were observed in approximately one-third of patients, indicating that anti-Ku antibody-positive ILD is not restricted to a single imaging phenotype. Pathologically, pure UIP was found in only one patients, whereas most biopsied patients featured NSIP or NSIP + OP as the predominant pattern. However, several patients exhibited unclassifiable patterns with partial UIP components, indicating that mixed histological patterns are common in anti-Ku antibody-positive ILD.

In fibrotic ILDs in general, radiological and/or histological UIP features have been associated with the development of PPF and poor prognosis [14–17]. In agreement with these reports, our patients with radiological or pathological UIP features tended to develop progressive fibrotic disease or acute exacerbation. Our findings are consistent with prior reports and suggest that, even when UIP is not the dominant pattern, the presence of UIP components might indicate an increased risk of disease progression in anti-Ku antibody-positive ILD. Comprehensive assessment integrating imaging, pathology, and clinical course is therefore crucial when determining treatment strategies.

In the study by Laure et al., all patients with anti-Ku antibody-positive ILD were diagnosed with CTDs, whereas our cohort included patients diagnosed with IIPs. We did not observe a clear difference in the degree of fibrotic progression between CTD-ILD and IIP cases. In agreement with our findings, Céline et al. described progressive respiratory failure in patients with anti-Ku antibody-positive ILD who did not meet the CTD criteria [18]. Furthermore, even when patients with IIP were stratified by the presence or absence of systemic symptoms and/or UIP features (Table 5), both groups displayed progressive fibrosis or PPF, indicating that the presence of systemic symptoms alone might not be sufficient to stratify the risk of progression.

Table 5
Baseline Features in ILD associated with anti-Ku antibody: CTD vs. Non-CTD

Variable	CTD	non-CTD (A + B)	A: non-CTD (any clinical features)	B: non-CTD (no clinical features)
	n = 7	n = 6	n = 3	n = 3
Female	4 (57.1)	2 (33.3)	1 (33.3)	1 (33.3)
Male	3 (42.9)	4 (66.7)	2 (66.7)	2 (66.7)
Age	62.6 (45.0–73.0)	65.5 (32.0–85.0)	52.0 (32.0–69.0)	79.0 (74.0–85.0)
Smoking	2 (28.6)	2 (33.2)	0	2 (66.7)
Clinical features	6 (85.7)	3 (50.0)	3 (100)	0
Radiological UIP features*	4 (57.1)	1 (16.7)	0	1 (33.3)
Pathological UIP features*	3 (42.9)	2 (16.7)	0	1 (33.3)
IP-AE	3 (42.9)	3 (16.7)	0	1 (33.3)
PPF	2 (28.6)	2 (33.3)	1 (33.3)	1 (33.3)

CTD, connective tissue disease; UIP, usual interstitial pneumonia; AE, acute exacerbation; PPF, progressive pulmonary fibrosis.

* UIP features indicate UIP-like components and do not necessarily represent a predominant UIP pattern.

The mechanisms linking anti-Ku antibodies to disease progression remain unclear. However, as Ku proteins are involved in DNA double-strand break repair and telomere maintenance [18–20], any defect in these pathways can contribute to cellular senescence, chronic inflammation, and fibrogenesis. In vitro, cells lacking Ku proteins exhibit telomere shortening, which has been associated with the development and progression of IPF [21, 22]. Although telomere length was not evaluated in our study, the occurrence of progressive fibrosis even in patients with few systemic manifestations suggests that a shared fibrotic susceptibility might exist in a subset of anti-Ku antibody-positive ILD.

Antifibrotic agents were used in three patients. No serious adverse events were observed, and in some cases, stabilization of FVC decline was achieved. However, the number of treated patients was small, and these observations should be interpreted as exploratory. Further studies are needed to determine the efficacy and optimal timing of antifibrotic therapy in anti-Ku antibody-positive ILD.

This study had several limitations. First, this was a retrospective study with potential biases and an inability to assess the effects of comorbidities and other confounding factors on patient outcome. Second, the sample size was small, the observation period was limited. Third, the study was conducted at a single center, which might significantly affect the generalizability of the findings. Fourth, only some patients were evaluated by rheumatologists at the initial visit, and thus, the diagnosis of CTDs might have been delayed in some cases. Fifth, lung biopsy was performed at the discretion of the treating physicians, which potentially introduced selection bias. Finally, this was an observational study; therefore, causal relationships cannot be confirmed, and our findings should be interpreted with caution.

5. Conclusions

We reported a case series of 13 patients with anti-Ku antibody-positive ILD and comprehensively evaluated their clinical characteristics, imaging findings, pulmonary function, histopathology, clinical course, and outcomes. In this cohort, some patients developed lung involvement before the CTD diagnosis, and others remained classified as IIPs without CTDs during the observation period. These suggests that anti-Ku antibody positivity does not necessarily indicate a typical CTD-associated ILD phenotype.

A subset of patients developed progressive fibrotic disease regardless of their CTD status, and radiological or pathological UIP features tended to be associated with fibrotic progression or acute exacerbation. Collectively, our findings indicate that patients with anti-Ku antibody-positive ILD require careful follow-up with attention to both the potential development of CTDs and PPF. Individualized treatment strategies, including appropriate use of anti-inflammatory and antifibrotic therapies, should be considered according to patients' clinical, radiological, and pathological phenotypes.

Abbreviations

CTD
connective tissue diseases
FVC
forced vital capacity
GGO
ground-glass opacities
HRCT
high-resolution computed tomography
IIP
idiopathic interstitial pneumonias

ILD
interstitial lung disease
IPF
idiopathic pulmonary fibrosis
UIP
usual interstitial pneumonia
OP
organizing pneumonia
NSIP
nonspecific interstitial pneumonia
PPF
progressive pulmonary fibrosis
MCTD
mixed connective tissue disease
RA
rheumatoid arthritis
IIM
idiopathic inflammatory myopathy

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and in adherence to the STROBE statement. This study was approved by the institutional ethics committee of [Saitama Red Cross Hospital] (approval number: [25-Y], date; September-24-2025), and the requirement for informed consent was waived because of its retrospective design.

Consent for publication

Not applicable.

Competing Interests

H.Y. and S.S. received honoraria from Nippon Boehringer Ingelheim Co., Ltd. The other authors have no conflicts of interest.

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Author Contribution

D.N., H.Y., and H.M. contributed to the conception and design of the current study. D.N., H.O., S.S., A.A., T.T., M.A., and H.M. contributed to data acquisition and investigation. H.Y. performed the formal analysis and interpretation of the data. D.N. drafted the original manuscript, and all authors contributed to critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data Availability

Datasets generated and/or analyzed during the current study are not publicly available due to the inclusion of sensitive patient information but are available from the corresponding author on reasonable request.

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Figures

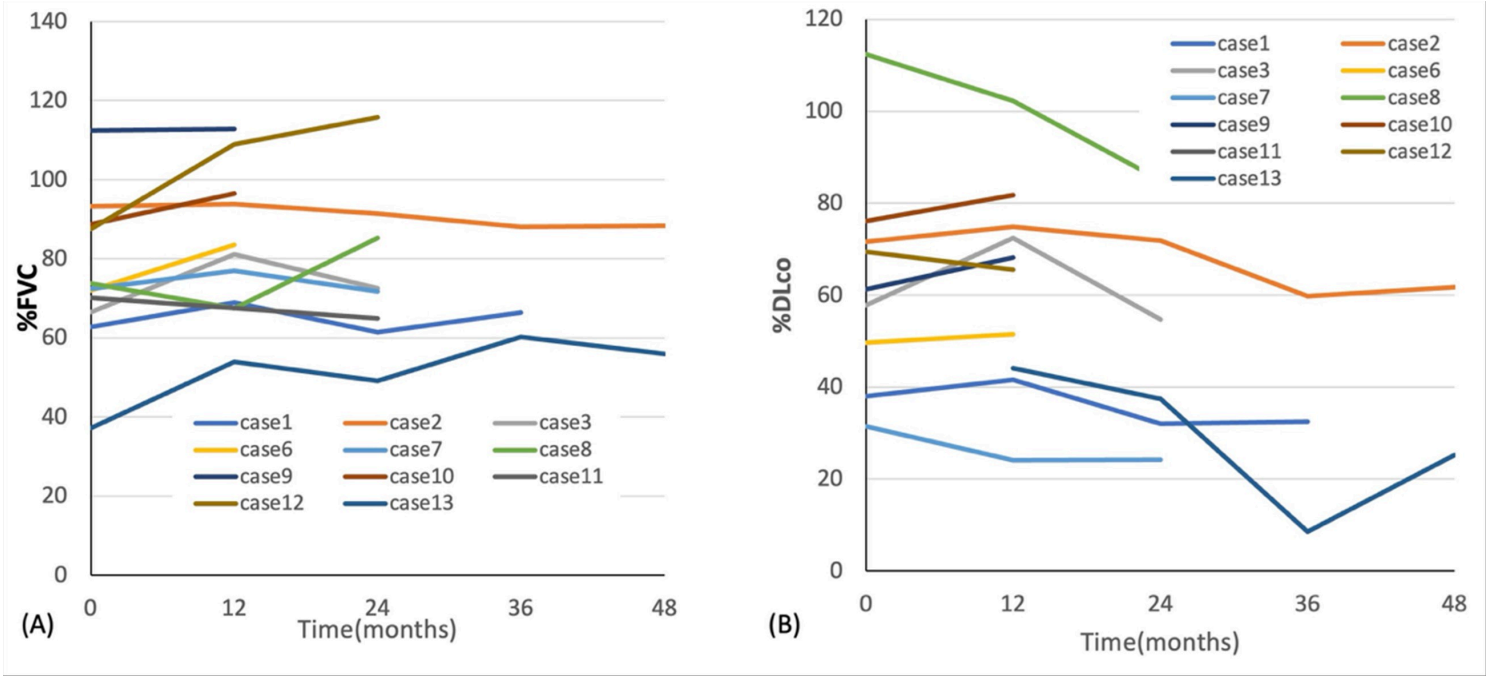


Figure 1

Longitudinal changes in pulmonary function.

(A) Temporal changes in percent predicted forced vital capacity (%FVC).

(B) Temporal changes in percent predicted diffusing capacity of the lungs for carbon monoxide (%DL_{CO}).

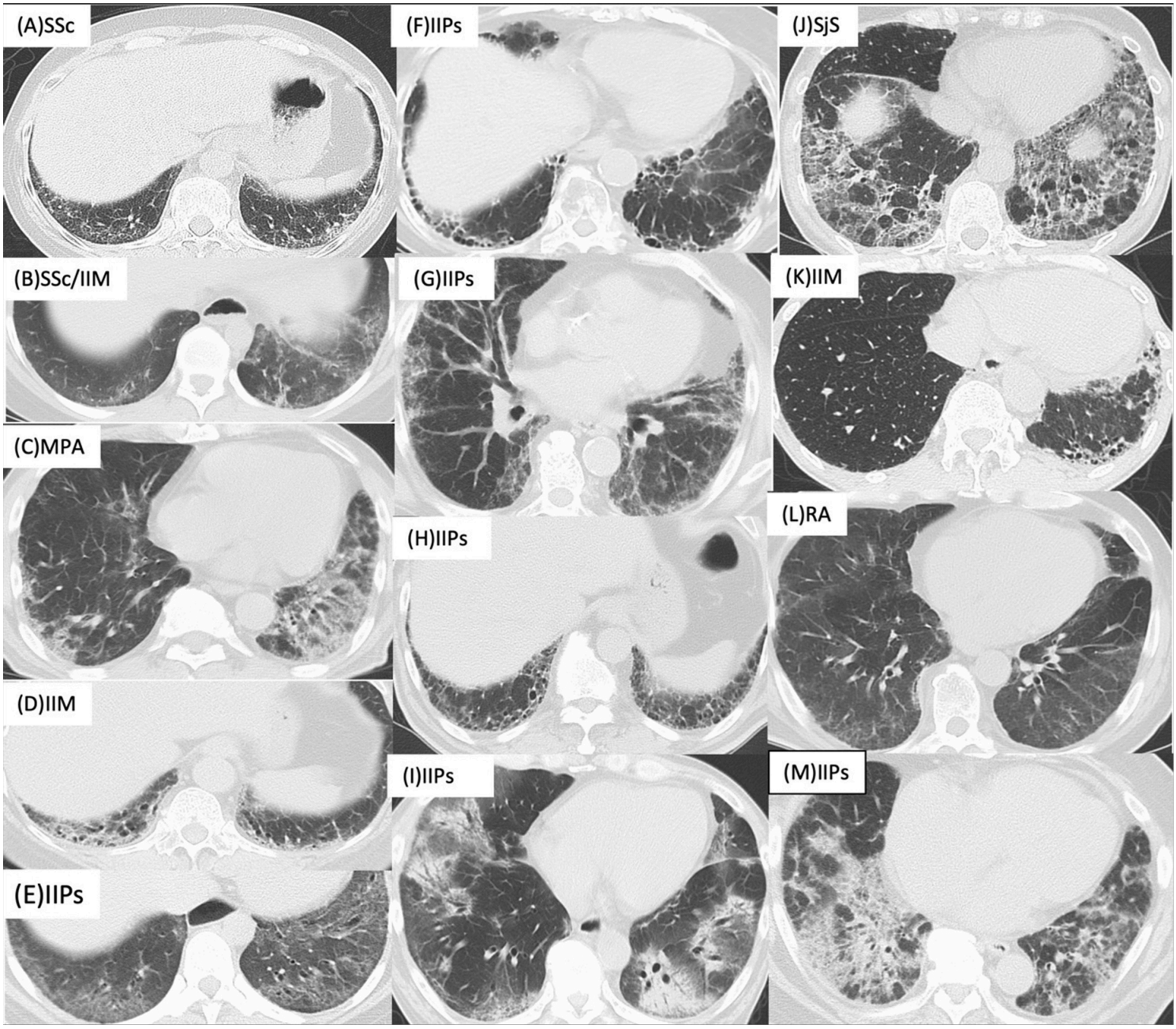


Figure 2

Representative high-resolution computed tomography (HRCT) findings in 13 patients with anti-Ku antibody-positive interstitial lung disease.

(A) Case 1, probable usual interstitial pneumonia (UIP) pattern with basal-predominant reticulation without honeycombing.

(B) Case 2, nonspecific interstitial pneumonia (NSIP) pattern with ground-glass opacities (GGOs) and consolidation along the bronchovascular bundles.

(C) Case 3, unclassifiable pattern with GGOs, contraction-associated consolidation, and subpleural reticulation.

(D) Case 4, probable UIP pattern with subpleural reticulation and bronchiolectasis.

(E) Case 5, NSIP pattern with GGOs and bronchiolectasis along the bronchovascular bundles.

(F) Case 6, unclassifiable pattern with subpleural reticulation and mild honeycombing.

(G) Case 7, NSIP pattern with peribronchovascular GGOs and traction bronchiolectasis.

(H) Case 8, probable UIP pattern with subpleural reticulation and bronchiolectasis.

(I) Case 9, NSIP with organizing pneumonia pattern with multiple contracting consolidations and GGOs.

(J) Case 10, NSIP pattern with GGOs and reticulation along the bronchovascular bundles.

(K) Case 11, probable UIP pattern with subpleural reticulation and bronchiolectasis in the left lower lobe.

(L) Case 12, NSIP pattern with GGOs along the bronchovascular bundles.

(M) Case 13, unclassifiable pattern with peribronchovascular GGOs and contraction-associated consolidation.

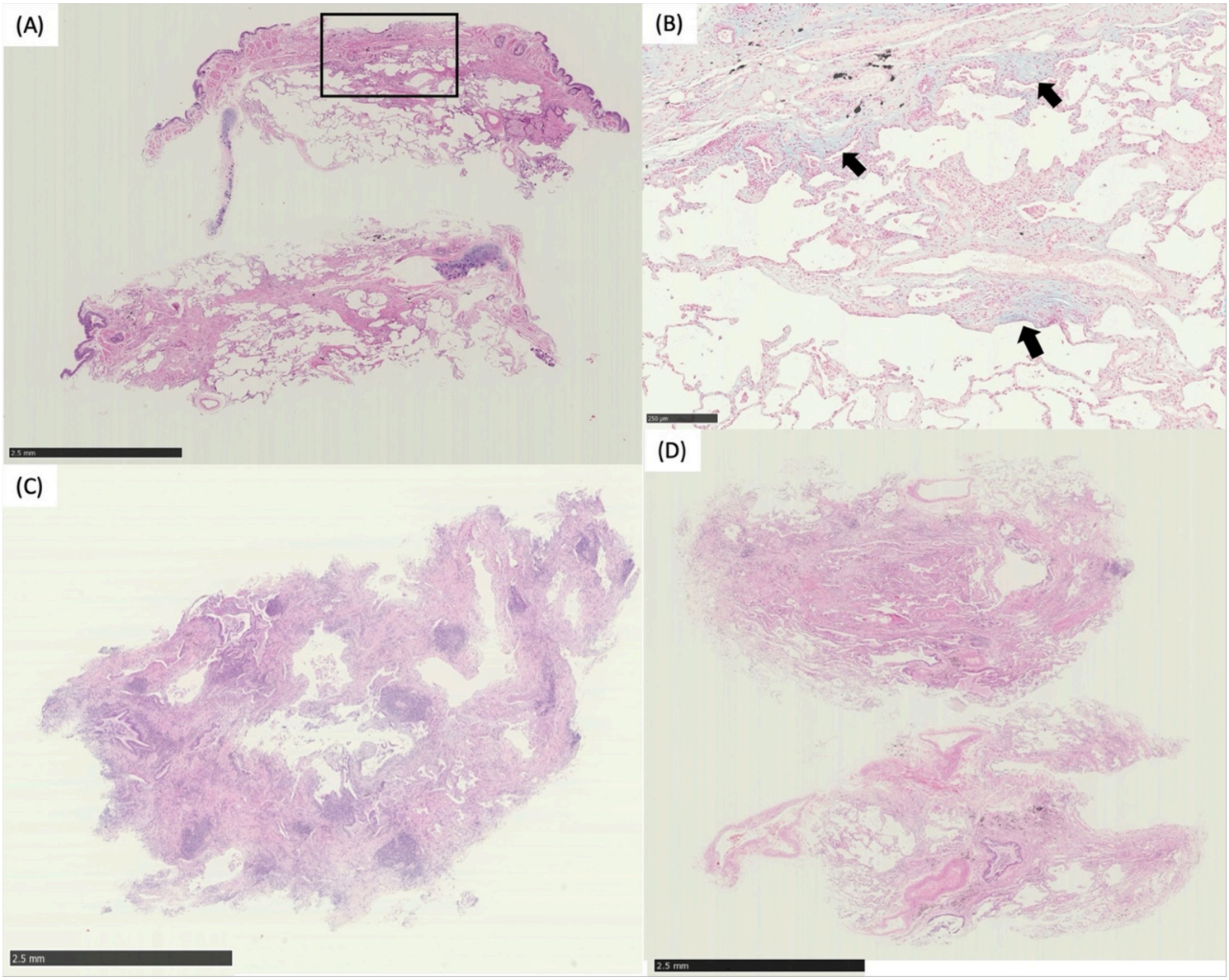


Figure 3

Histopathological findings in three cases of anti-Ku antibody-positive interstitial lung disease.

(A) Case 3: A 73-year-old man who developed microscopic polyangiitis (MPA). The TBLC specimen from the left B^8 shows perilobular fibrosis with focal lymphocyte infiltration. (Hematoxylin–eosin (H&E) stain, scale bar = 2.5 mm)

(B) A square area of (A) highlights fibroblastic foci (arrows). (Alcian blue-PAS stain, scale bar = 250 μm)

(C) Case 10: A 57-year-old man who developed Sjögren's syndrome (SjS). The specimen taken from right B^9b shows marked interstitial and intra-alveolar fibrosis with cystic changes, occasional fibroblastic foci, and lymphoid follicles. (H&E stain, scale bar = 2.5 mm).

(D) Case 13: A 69-year-old man. The TBLC specimen from right B^2 shows diffuse alveolar wall fibrosis with occasional collapsed intra-alveolar fibrosis, consistent with NSIP + OP. (H&E stain, scale bar = 2.5 mm).