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Clinico-radio-pathological characteristics of unclassifiable idiopathic interstitial pneumonias

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ABSTRACT

Background: The purpose of this study was to clarify the clinico-radio-pathological characteristics and prognostic factors of unclassifiable-idiopathic interstitial pneumonias (U-IIPs) diagnosed by surgical lung biopsy.

Methods: Among 86 patients with interstitial pneumonia who underwent surgical lung biopsy from January 2005 to September 2013, 33 (38.4%; 16 male patients; mean age, 64.4 ± 8.8 years) were diagnosed with U-IIPs. They were subsequently categorized into rapidly progressive ($n = 7$), slowly progressive ($n = 7$), and stable ($n = 19$) groups based on the decrease of the percent predicted forced vital capacity or percent predicted diffusing capacity of the lung carbon monoxide and the occurrence of acute exacerbation. The clinico-radio-pathological features and survival rates of the patients who were followed up for at least 3 years were examined. These cases were reevaluated retrospectively by multidisciplinary discussion.

Results: The rapidly progressive group had a significantly poorer prognosis than that of the other groups ($p < 0.0001$). Although there were no significant pattern differences on the chest high-resolution computed tomography, the fibrosis scores were significantly higher in the rapidly progressive group ($p = 0.002$). Furthermore, the percentage of fibroblastic foci assessed by the pathological analysis was also significantly higher in the rapidly progressive group ($p = 0.006$). Nine (27.3%) patients developed connective tissue diseases during follow-up.

Abbreviations: CF, centrilobular fibrosis; CHP, chronic hypersensitivity pneumonitis; CVD-IP, collagen vascular disease-related interstitial pneumonia; DLco, diffusing capacity of the lung carbon monoxide; FF, fibroblastic foci; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonias; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; MPA, microscopic polyangiitis; NSIP, idiopathic nonspecific interstitial pneumonia; PPFE, idiopathic pleuroparenchymal fibroelastosis; SLB, surgical lung biopsy; U-IIP, unclassifiable-idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia

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Conclusions: The radiologic patterns were not significantly different among the three clinical U-IIPs subgroups. Nevertheless, our findings suggested that the fibrosis scores and the percentage of fibroblastic foci could provide a prognostic assessment in U-IIPs.

1. Introduction

According to the 2013 American Thoracic Society/European Respiratory Society classification system, idiopathic interstitial pneumonias (IIPs) are now divided into three categories: (1) major IIPs, including idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia; (2) rare IIPs, including idiopathic lymphoid interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis (PPFE); and (3) unclassifiable IIPs (U-IIPs) [1].

The appropriate classification of IIPs requires a multidisciplinary approach with inputs from experienced pulmonologists, chest radiologists, and lung pathologists. As a result, some patients cannot be classified into a specific diagnostic category owing to overlapping histopathological features and major discrepancies among the clinical, radiological, and histologic features.

Ryerson et al. [2] reported that the incidence of the unclassifiable interstitial lung disease (ILD) was almost 10% ($n = 132$) in a cohort of 1370 patients with ILD. The most common reason for the diagnosis of unclassifiable ILD was the missing histopathological assessment owing to the high risk of surgical lung biopsy (SLB) or patient unwillingness. Therefore, to date, the clinico-radio-pathological characteristics of U-IIPs diagnosed by SLB have not been characterized clearly. The purpose of this study was to clarify the clinico-radio-pathological features and prognostic factors of U-IIPs diagnosed by a multidisciplinary approach.

2. Materials and methods

This study was approved by our institutional review board on July 28, 2016 (Toho University Omori Medical Center ethical committee; approval number M16074). Written informed consent for the study protocols was obtained from all patients (including a general informed consent).

We had a multidisciplinary discussion (MDD) conference with experienced radiologists and lung pathologists in Toho University Omori Medical Center and sequentially discussed and reevaluated approximately two U-IIPs cases, which had been diagnosed as U-IIPs at the previous MDD conference, once every two months since September 2013 according to the 2013 American Thoracic Society/European Respiratory Society classification system [1]. The reason for the diagnosis of U-IIPs is the major discrepancy among the clinical, radiological, histological features in all cases due to the presence of overlapping or concurrent histological features.

2.1. Patients

The medical records of 86 patients with interstitial pneumonia who underwent SLB at our hospital between January 2005 and September 2013 were retrospectively examined, and a total of 33 patients (38.4%; 16 males, 17 females; mean age, 64.4 ± 8.8 years) diagnosed with U-IIPs were identified. Other diagnoses included IPF ($n = 23$, 26.7%), NSIP ($n = 21$, 24.1%), chronic hypersensitivity pneumonitis (CHP) ($n = 5$, 5.8%), cryptogenic organizing pneumonia ($n = 2$, 2.3%), and PPFE ($n = 2$, 2.3%).

Patients with U-IIPs in this cohort were retrospectively categorized into three groups. The rapidly progressive group included patients with more than 10% decrease in the percent predicted forced vital capacity (%FVC), more than 15% decrease in the percent predicted diffusing capacity of the lung carbon monoxide (%DLco), or acute exacerbation within 12 months after diagnosis ($n = 7$). The slowly progressive group included patients with 5–10% decrease in %FVC, 10–15% decrease in %DLco, or acute exacerbation within 24 months compared with evaluations from 6 months earlier ($n = 7$). The stable group included patients who did not meet any of the criteria based on %FVC and %DLco within 24 months ($n = 19$). The clinico-radio-pathological features and survival rates of the patients who were followed up for at least 3 years (median, 60.5 ± 56.6 months) were examined.

Acute exacerbation of IIPs was defined according to the Japanese criteria [3] during chronic clinical course of IIPs as follows: (1) exacerbation of dyspnea within a month, (2) newly developing bilateral density elevation on high-resolution computed tomography (HRCT) scans, and (3) deterioration of hypoxemia (decrease of PaO_2 more than 10 mmHg under similar conditions). The gender (sex), age, and physiology (GAP) index was evaluated [4]. The cumulative amount of tobacco consumption expressed as the smoking index was defined as the number of cigarettes consumed per day multiplied by the years of smoking [5].

2.2. Clinical approach

We evaluated the results of the (1) serum marker tests including the Krebs von den Lungen-6, surfactant protein D, antinuclear antibody, and auto-antibodies related to connective tissue diseases, (2) pulmonary function tests (Chestac-33, CHEST Co. Ltd, Tokyo, Japan), (3) chest helical CT scans (Aquilion 16, Toshiba, Tokyo, Japan), and (4) Doppler echocardiography at initial admission for preoperative inspection. We also surveyed the classification criteria for interstitial pneumonia with autoimmune features (IPAF) prior to surgery [6]. We reviewed the records to ensure that the follow-up evaluations with the pulmonary function tests were performed every 3–6 months, similar to those done for IPF.

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Table 1 – Baseline clinical characteristics of the study population.

Variable	Stable (n = 19)	Slowly progressive (n = 7)	Rapidly progressive (n = 7)	p-value
Sex (M/F)	8/11	4/3	4/3	0.69
Age (years)	64.3 ± 8.8	64.9 ± 7.0	64.4 ± 11.6	0.84
Smoking index[a]	528.7 ± 503.8	327.9 ± 440.9	357.1 ± 525.5	0.64
GAP score	1.8 ± 1.0	2.7 ± 1.4	3.6 ± 2.2	0.13
IPAF (n)	7/19 (36.8%)	0/7 (0%)	0/7 (0%)	0.06
%FVC (%)	92.1 ± 18.5	90.1 ± 24.8	80.3 ± 23.4	0.27
FVC (L)	2.6 ± 0.8	2.8 ± 1.1	2.5 ± 1.3	0.69
$\%FEV_1$ (%)	97.7 ± 12.1	92.6 ± 22.1	88.8 ± 16.6	0.67
FEV_1 (L)	2.0 ± 0.6	2.3 ± 0.8	2.1 ± 1.0	0.76
%DLco (%)	70.6 ± 18.8	64.5 ± 12.5	66.9 ± 21.3	0.85
%DLco/VA (%)	83.2 ± 15.0	72.8 ± 16.2	88.2 ± 19.6	0.23
CPI	29.6 ± 16.2	32.8 ± 11.7	35.1 ± 17.1	0.45
esPAP (mmHg)	30.5 ± 6.9	29.6 ± 5.9	30.4 ± 4.7	0.59
KL-6 (U/ml)	876.1 ± 564.4	1111.3 ± 505.2	2273.3 ± 3020	0.26
SP-D (ng/ml)	191.6 ± 123.6	260.1 ± 74.3	368.2 ± 328.3	0.12
Anti-nuclear Ab (x)	44.2 ± 39.8	28.6 ± 30.2	28.6 ± 30.2	0.52
Acute exacerbation (n)	4/19 (21.1%)	2/7 (28.6%)	4/7 (57.1%)	0.29

Data are presented as mean ± standard deviation.
Ab, antibody; CPI, composite physiologic index; DLco, diffusing capacity of the lung carbon monoxide; esPAP, estimated systolic pulmonary arterial pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, gender, age, and physiologic variables; IPAF, interstitial pneumonia with auto immune features; KL-6, Kreb von den Lungen-6; SP-D, surfactant protein D; VA, alveolar volume.
[a] Smoking index, number of cigarettes consumed per day multiplied by years of smoking.

The composite physiological index was calculated using the following formula: [91 − (0.65 × %DLco) − (0.53 × %FVC) + (0.34 × percent predicted forced expiratory volume in one second)] [7].

2.3. *Radiological approach*

Routine scanning of the entire lung was performed with a slice thickness of 5–10 mm, followed by HRCT images with a 1–2 mm section thickness at full inspiration (120 kVp, 300 mA, pitch 1.0).

The extent of fibrosis was visually assessed and quantified on the chest HRCT. The fibrosis scores (total, 25 points) on HRCT were calculated from the sum of scores from all five lung lobes (right upper, right middle, right lower, left upper, and left lower lobes) [8] and were independently assessed by two pulmonologists (Y.N. and K.S.) and one radiologist (K.M.). Suggestive radiological patterns, such as a possible usual interstitial pneumonia (UIP) pattern and an inconsistent with UIP pattern, were classified based on the HRCT findings in accordance with the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement [9].

2.4. *Pathological approach*

Lung tissue specimens were obtained by SLB from at least two different sites. A total of 75 specimens were obtained from the 33 patients included in this study. All cases were reviewed and scored retrospectively by two pathologists (A. H., M.K.) who were unaware of the clinical and physiological findings. Each pathologist received two slides from each specimen block: one stained with hematoxylin and eosin and one stained with Elastica van Gieson. The slides were categorized according to the fibrosis patterns [9] and were evaluated for the presence of fibroblastic foci (FF). Subsequently, two pathologists reviewed all the lung biopsy specimens and provided a semi-quantitative score to reflect the FF percentage (%FF) by using a visual four-point scale (0 for the absence of FF, and 1, 2, and 3 for %FF of 0–25%, 25–50%, and ≥ 50%, respectively). Additionally, the presence of 13 histopathological factors was assessed: bronchial metaplasia, organizing pneumonia, pleuritis, lymphoid follicles with germinal center, plasmacytic infiltration, centrilobular fibrosis (CF), granuloma, vasculitis, thickening of the muscular media indicating pulmonary hypertension, apical cap, emphysema, diffuse alveolar damage, and pulmonary alveolar proteinosis-like lesions.

2.5. *Statistical analysis*

Comparisons among the U-IIPs groups were performed by using the Kruskal-Wallis rank sum and Steel-Dwass tests. Fisher's exact test was used for the comparison of the categorical variables. The survival rate was calculated by the Kaplan-Meier method, and the log-rank test was used with the significance level set at < 0.05. Data were expressed as means ± standard deviation. All p values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [10].

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3. Results

3.1. Clinical analysis

There were no significant differences in the demographic and baseline characteristics among the three groups categorized according to the severity of U-IIPs (Table 1). The frequency of acute exacerbation tended to be higher in the rapidly progressive group, but was not significantly different than the other two groups (stable, $n = 4$, 21.1%; slowly progressive, $n = 2$ [28.6%]; rapidly progressive, $n = 4$ [57.1%]; $p = 0.29$). The major causes of death were acute exacerbation ($n = 7$, 41.2%), primary lung cancer ($n = 2$, 11.8%), bacterial pneumonia ($n = 1$, 5.9%), diffuse alveolar hemorrhage ($n = 1$, 5.9%), and other ($n = 6$, 35.3%). There was no significant difference in the treatment modalities among the groups. However, there was a tendency to use steroid and immunosuppressive combination therapy more frequently in the rapidly progressive group than in the other groups, while antifibrotic agents such as nintedanib and pirfenidone tended to be used relatively later (Table 2). The stable group tended to have a longer latency until the primary treatment than the other groups (Table 3). Patients in the rapidly progressive group had a significantly worse prognosis than those in the other groups ($p < 0.0001$, Fig. 1).

Retrospectively, the final diagnoses by MDD were U-IIP ($n = 18$, 54.5%), collagen vascular disease-related interstitial pneumonia (CVD-IP; $n = 9$, 27.3%), CHP ($n = 3$, 9.1%), PPFE ($n = 2$, 6.1%), and IPF with emphysema (n = 1, 3.0%). During the final MDD, we made a diagnosis of CHP based on disease behaviors such as spontaneous remission and seasonal progression and on pathological findings such as centrilobular fibrosis or granuloma.

Nine patients (27.3%) were diagnosed with CVD-IP during follow-up, which included rheumatoid arthritis ($n = 3$), systemic sclerosis ($n = 1$), dermatomyositis ($n = 1$), and microscopic polyangiitis (MPA, $n = 4$). Among these, eight patients (88.9%) belonged to the stable group and six patients (66.7%) met the criteria of IPAF prior to surgery, whereas three other patients fulfilled at least one criterion among the clinical, serological, and morphological domains. In the final diagnosis, there were no significant differences in the prognosis between CVD-IP and U-IIP ($p = 0.67$), but patients in the CVD-IP group met the criteria of IPAF prior to surgery more significantly than those in the U-IIP group (CVD-IP, $n = 6$, 66.7%; U-IIP, $n = 1$, 5.6%: $p = 0.002$).

Table 2 – Administered treatment.

Patient group according to disease progression	Medication	First line	Second line	Third line
Rapid ($n = 7$)	PSL	2/7	1/7	
	PSL + CyA	1/7		
	mPSL pulse	2/7		
	mPSL pulse + CyA	2/7		
	CyA		1/7	
	TAC		1/7	1/5
	IVCY			1/5
	NAC		2/7	
	PFD		1/7	1/5
	HOT		1/7	2/5
Slow ($n = 7$)	Observation	1/7		
	PSL		3/6	
	mPSL pulse	2/7		
	CyA			1/4
	NAC	3/7	3/6	
	PFD			1/4
	Nintedanib			1/4
	HOT			1/4
	SOD	1/7		
Stable ($n = 19$)	Observation	4/19		
	PSL	5/19	6/10	
	mPSL pulse	5/19		1/6
	CyA			1/6
	TAC		2/10	
	IVCY			1/6
	NAC	3/19		1/6
	PFD	1/19	1/10	1/6
	HOT	1/19	1/10	1/6

CyA, cyclosporin A; HOT, home oxygen therapy; IVCY, intermittent pulse intravenous cyclophosphamide therapy; NAC, N-acetylcysteine; PFD, pirfenidone; PSL, prednisolone; SOD, superoxide dismutase; TAC, tacrolimus.

3.2. Radiological analysis

The fibrosis scores on HRCT were significantly higher in the rapidly progressive group (stable *vs.* slowly *vs.* rapidly: 4.7 ± 1.8 *vs.* 7.0 ± 1.6 *vs.* 7.7 ± 2.1; $p = 0.002$). As evidenced by the chest HRCT, 12 patients exhibited a possible UIP pattern, whereas 21 patients showed a pattern inconsistent with UIP. Among these latter, ground glass opacity (n = 11), consolidation (n = 5), organizing pneumonia (n = 3), multiple nodules (n = 3), and large cysts (n = 1) were found (included overlapping features); there were no significant differences in the chest HRCT patterns among the three groups (Fig. 2).

3.3. Pathological analysis

Based on the pathological analysis, 31 patients were diagnosed as "not UIP." CF was the primary reason for the "not

Table 3 – Duration until first line therapy and clinical course.

Variable	Stable (n = 19)	Slowly progressive ($n = 7$)	Rapidly progressive ($n = 7$)	p-Value
Duration until first line (months)	27.9 ± 36.4	16.0 ± 15.5	5.4 ± 9.2	0.36
Disease progression (months)	67.6 ± 28.7	17.4 ± 4.3	6.4 ± 3.9	< 0.0001
Survival time (months)	79.8 ± 29.4	46.8 ± 18.4	21.6 ± 10.6	0.0001

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UIP" diagnosis in this study (Fig. 3). The pathological causes for the unclassifiable ILD were CF (n = 22, 40%), NSIP overlap (n = 13, 23.6%), PPFE-like (n = 6, 10.9%), lymphoid follicles with germinal center (n = 6, 10.9%), granuloma (n = 5, 9.1%), and irregular fibrosis (n = 3, 5.5%) (Fig. 4). The remaining two patients were diagnosed as "possible UIP" by pathological analysis. However, the radiological findings in these cases were inconsistent with the UIP pattern. Thus, we diagnosed these two patients with U-IIP at the final MDD because of the major discrepancies among the clinical, radiological, histological features.

The pathological analysis revealed that the %FF was significantly higher in the rapidly progressive group than in the other two groups (stable *vs.* slowly *vs.* rapidly: 0.9 ± 0.8 *vs.* 1.6 ± 1.3 *vs.* 2.4 ± 0.8; p = 0.006). There were no significant differences in 11 of the 13 histopathological factors evaluated in this study (Table 4). Vasculitis and diffuse alveolar damage were not detected in any of the cases.

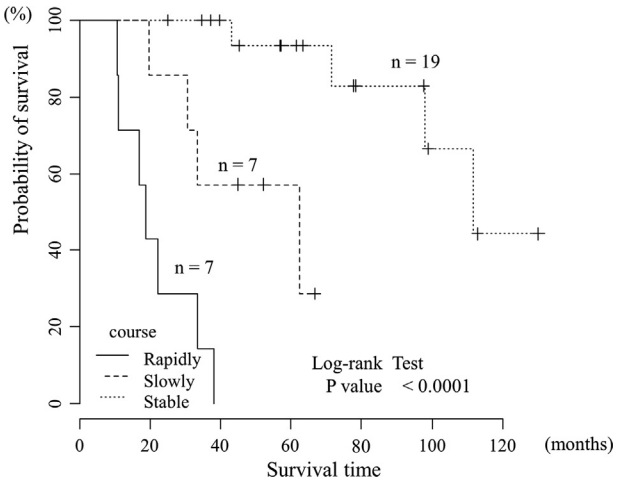

Fig. 1 – The Kaplan-Meier survival curve in patients with rapidly progressive (n = 7), slowly progressive (n = 7), and stable disease (n = 19). Survival time was significantly shorter in the rapidly progressive group than in the other two groups (median survival time [stable *vs.* slowly *vs.* rapidly]: 73.0 months *vs.* 56.4 months *vs.* 18.6 months; log-rank test, p < 0.0001).

4. Discussion

Despite several reports on U-IIPs since its definition in the international guidelines in 2013, much remains unsolved. A review by Skolnik and Ryerson [11] emphasized that the indicator "provisional" should be used to distinguish reports in which a biopsy was performed, given that clinically atypical images were commonly diagnosed as unclassifiable ILD even in cases in which histological examinations were difficult to perform for various reasons (e.g., poor health

Pathological reasons for unclassifiable ILD

	Rapidly (n = 7)	Slowly (n = 7)	Stable (n = 19)	p value
CF	5/2	6/1	11/8	0.48
NSIP overlap	3/4	1/6	9/10	0.38
PPFE like	2/5	3/4	1/18	0.048
LY	1/6	2/5	3/16	0.83
Granuloma	1/6	2/5	3/16	0.57
Irregular fibrosis	0/7	0/7	3/16	0.56

Fisher's exact test

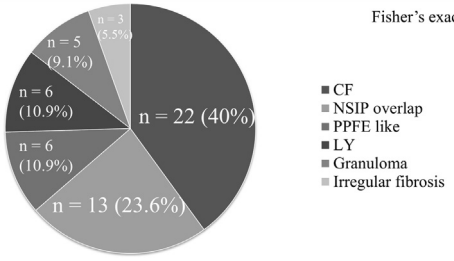

Fig. 3 – Based on the pathological analysis, 32 patients were diagnosed as "not usual interstitial pneumonia (UIP)." Centrilobular fibrosis (CF) was the primary cause of a "not UIP" diagnosis in this study. LY, lymphoid follicle with germinal center; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis.

	Possible UIP	GGO	Consolidation	OP	Multiple nodules	Large cysts
Rapidly (n = 7)	2	3	2	0	1	0
Slowly (n = 7)	3	1	3	0	0	0
Stable (n = 19)	7	7	0	3	2	1

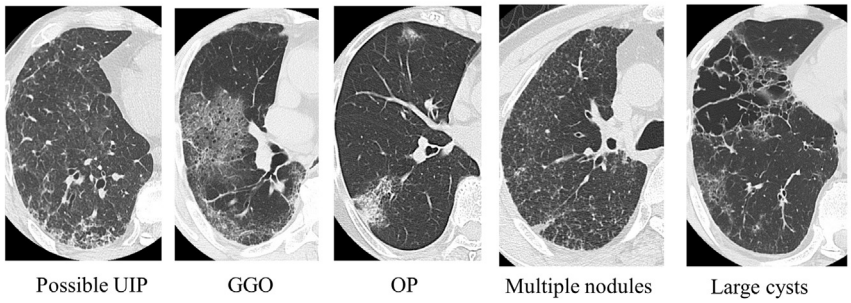

Fig. 2 – As evidenced by the chest high-resolution computed tomography, 12 patients exhibited a possible usual interstitial pneumonia (UIP) pattern, whereas 21 patients showed a pattern inconsistent with UIP. These consisted of ground glass opacity (GGO, n = 11), consolidation (n = 5), organizing pneumonia (OP, n = 3), multiple nodules (n = 3), and large cysts (n = 1), included overlapping features.

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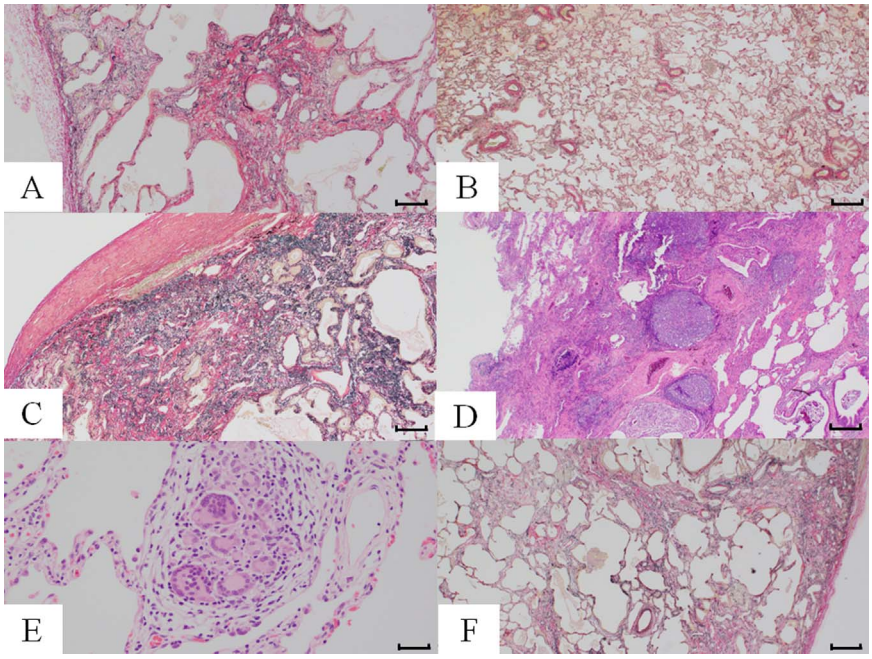

Fig. 4 – The pathological causes for the "not usual interstitial pneumonia (UIP)." (A) CF (EVG stain; objective ×4, scale bar = 200 μm). (B) NSIP (EVG stain; objective ×2, scale bar = 500 μm). (C) PPFE-like (EVG stain; objective ×4, scale bar = 200 μm). (D): LY (HE stain; objective ×2, scale bar = 500 μm). (E) Granuloma (HE stain; objective ×20, scale bar = 50 μm). (F) irregular fibrosis (EVG stain; objective ×2, scale bar = 500 μm). CF, centrilobular fibrosis; LY, lymphoid follicle with germinal center; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis.

Table 4 – Pathological findings.

Variable	Stable (n = 19)	Slowly progressive (n = 7)	Rapidly progressive (n = 7)	p-Value
FF	0.9 ± 0.8	1.6 ± 1.3	2.4 ± 0.8	0.006
BM	12/19	3/7	5/7	0.63
OP	4/19	1/7	0/7	0.80
PL	7/19	3/7	1/7	0.61
LY	14/19	4/7	5/7	0.87
PI	8/19	2/7	3/7	0.89
CF	12/19	6/7	5/7	0.69
GR	6/19	3/7	3/7	0.70
VA	0/19	0/7	0/7	–
PH	5/19	0/7	0/7	0.19
AP	3/9	4/5	2/4	0.44
EM	0/19	1/7	1/7	0.17
DAD	0/19	0/7	0/7	–
PAP	0/19	0/7	1/7	0.42

Date are presented as mean ± standard deviation.
AP, apical cap; BM, bronchial metaplasia; CF, centrilobular fibrosis; DAD, diffuse alveolar damage; EM, emphysema; FF, fibroblastic foci; GR, granuloma; LY, lymphoid follicle with germinal center; OP, organizing pneumonia; PAP, pulmonary alveolar proteinosis like lesion; PH, thickening of muscular media indicating pulmonary hypertension; PI, plasmacytic infiltration; PL, pleuritis; VA, vasculitis.

status of the patient, refusal of biopsy, stable status) [11]. There are several studies, such as that by Zhang et al. [12], in which the diagnosis was based on MDD after SLB for all cases to define ILD as unclassifiable; in other reports, the rate of SLB was low, between 22.7 and 34% [2,13–16]. Clearly, a large sample size is required to categorize these heterogeneous diseases under one definition. Therefore, we focused in this study on patients with SLB to examine retrospectively the clinico-radio-pathological features of U-IIPs.

The definition of disease progression in this study was based on a report by Ryerson *et al.* [2] and utilized the %FVC and %DLco values and the occurrence of acute exacerbation. We found that the prognosis was significantly worse in the rapidly progressive patients than in the other patients. Specifically, in the present study, the decrease in the respiratory function (i.e., %FVC and %DLco) and the occurrence of acute exacerbation were important prognostic factors that were independent of the subjective symptoms. To our knowledge, there are few reports about acute exacerbation in the unclassifiable ILD. We experienced acute exacerbation in 10 cases (30.3%) diagnosed with U-IIPs at the initial MDD. These patients had CVD-IPs such as microscopic polyangiitis, systemic sclerosis, dermatomyositis, and rheumatoid arthritis at the final MDD; we assumed that some of them were probably patients with early stage IPF. We also believe that acute exacerbations in U-IIPs are more common than previously thought. Therefore, strict 3- or 6-month follow-up evaluations with pulmonary function tests are critical in patients with U-IIPs. There was no significant difference in the treatment approaches among the groups; however, there was a tendency for a more frequent use of steroid and immunosuppressive combination therapy in the rapidly progressive group. Although the usefulness of nintedanib and pirfenidone as antifibrotic agents against IPF was reported [17], the timing of therapy initiation and their efficacy in U-IIPs remain controversial.

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In this study, the preoperative CT scans revealed no differences in the image patterns among the three groups, but significantly higher fibrosis scores on HRCT were observed in patients with rapid disease progression. The imaging characteristics varied widely among the patients with image patterns that were inconsistent with UIP and should be evaluated in future studies.

To our knowledge, this is the first study to examine U-IIPs histologically in detail. CF was the most frequent diagnosis for patients classified as "not UIP" in this study. While the diagnosis of "not UIP" that solely relies on the pathological assessment is problematic, there are currently no other established criteria to determine a lesion as "not UIP" and to assess the lesion progression. Clearly, cases designated as "not UIP" are difficult to distinguish from smoking-related disorders or CHP due to the common respiratory tract-related changes. The degree of FF by quantitative analysis was previously shown to reflect prognosis in patients with IPF [18]. In our study, the semi-quantitative analysis of %FF revealed that there was a tendency for higher %FF and myxoid changes in the rapidly progressive group, comparable to IPF, suggesting that %FF by SLB should be taken into consideration for diagnosis.

Interestingly, patterns indicative of NSIP and LY were observed more frequently in the stable group than in other groups. Furthermore, six of seven cases that met the IPAF criteria developed CVD-IP during follow-up. Thus, before performing SLB in patients meeting the IPAF criteria, detailed physical examination as well as periodical confirmation of serum markers and urinary tests should be conducted to evaluate the possible emergence of the collagen-related disease.

This study had several limitations. First, it was a single-center, retrospective study, with a small number of cases. A prospective multicenter study is thus necessary in future. Second, the quantitative analyses of the imaging and histopathological findings were limited. Unified diagnostic criteria are necessary in the pathological findings and should be used in the future. Finally, SLB was performed at a different timing for each case, which may influence the results.

5. Conclusions

The radiologic patterns were not significantly different among the three U-IIPs clinical subgroups. Nevertheless, our findings suggested that the fibrosis score on HRCT and the % FF on pathology could provide a prognostic assessment in U-IIPs. Future studies with a larger sample size are necessary to determine the treatment strategies and disease behavior for patients with unclassifiable ILD.

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Conflict of interest

The authors have no conflicts of interest to declare.

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