Radial Endobronchial Ultrasonography with a Guide Sheath for the Diagnosis of Diffuse Parenchymal Lung Diseases

CURRENT STATUS: POSTED

Minoru Inomata inomataminoru@nms.ac.jp
Corresponding Author
ORCiD: 0000-0003-4149-9779

Naoyuki Kuse
Nihon Sekijujisha

Nobuyasu Awano
Nihon Sekijujisha

Mari Tone
Nihon Sekijujisha

Hanako Yoshimura
Nihon Sekijujisha

Tatsunori Jo
Nihon Sekijujisha

Atsuko Moriya
Nihon Sekijujisha

Yuan Bae
Nihon Sekijujisha

Toshio Kumasaka
Nihon Sekijujisha

Tamiko Takemura
Nihon Sekijujisha

Takehiro Izumo
Nihon Sekijujisha

DOI: 10.21203/rs.2.12683/v1

SUBJECT AREAS
Pulmonology

KEYWORDS
ultrasonography, lung disease, interstitial, pulmonary fibrosis
Abstract

Background Radial-endobronchial ultrasonography (R-EBUS) is a useful bronchoscopic tool for the diagnosis of solitary pulmonary peripheral lesions. However, the utility of R-EBUS for the diagnosis of diffuse parenchymal lung disease (DPLD) remains unclear. This study aimed to examine the characteristics of R-EBUS patterns in association with computed tomography (CT) findings in diagnosing DPLD.

Methods Transbronchial lung biopsy (TBLB) was performed using R-EBUS and a guide sheath (GS) in consecutive 35 patients with suspected DPLD on chest CT between March–November 2017. Consolidation, ground glass opacity (GGO), reticular, and nodular patterns were diagnosed, and the mean CT Hounsfield units in the sampled area were measured in patients with consolidation. R-EBUS characteristics and their association with CT findings and pathological diagnostic yield were evaluated.

Results R-EBUS showed a dense pattern only in patients with consolidation, and a blizzard pattern in patients with consolidation, GGO, reticular, and nodular patterns on CT. The biopsied area’s mean CT value was significantly higher in patients with dense than with blizzard patterns (p < 0.0001), and pathological findings were also dense in patients with R-EBUS dense pattern. The pathological diagnostic yield was significantly higher in patients with overt R-EBUS patterns than in patients without R-EBUS patterns by obtaining better lung tissue samples with the GS (p < 0.0001).

Conclusions Dense and blizzard R-EBUS patterns were novel findings in diagnosing DPLD, and TBLB with R-EBUS-GS may be a valuable tool in diagnosing DPLD

Background

Diffuse parenchymal lung disease (DPLD) encompasses a large group of respiratory disorders and it can be challenging to identify its cause because various medical
conditions can mimic DPLD. According to the idiopathic pulmonary fibrosis (IPF) and idiopathic interstitial pneumonias guidelines, pathological diagnosis is essential for the diagnosis of interstitial lung disease (ILD) and IPF without honeycombing\cite{1, 2}. A precise diagnosis is needed for optimal treatment. Compared to surgical lung biopsy, transbronchial lung biopsy (TBLB) is a less invasive procedure; it is widely used and important for obtaining lung tissue samples for the pathological diagnosis of DPLD. Radial-endobronchial ultrasonography (R-EBUS) with a guide sheath (GS) (R-EBUS-GS) is widely used and is useful for the diagnosis of solitary pulmonary peripheral lesions\cite{3}. Reportedly, TBLB with R-EBUS-GS is a useful tool for ground glass nodules in lung cancer, whose characteristic R-EBUS signals are blizzard and mixed-blizzard patterns\cite{4}. However, the characteristics of R-EBUS in DPLD patients remain unknown\cite{5} and have yet to be evaluated for the diagnosis of DPLD. The pathological diagnostic yield for DPLD, especially for ILD, using only TBLB samples is not high; therefore, further R-EBUS-GS evaluation is needed to improve the diagnostic accuracy.

Methods

2.1 Subjects

This retrospective, single-center study aimed to examine the characteristics of R-EBUS patterns in association with CT findings in diagnosing DPLD. We conducted a retrospective review. Between March and November 2017, 35 consecutive patients who presented with suspected DPLD on chest CT underwent lung biopsy and bronchoscopic examination using R-EBUS-GS. The medical records of the study population were reviewed and evaluated. This study was approved on June 1, 2018 by the hospital’s Institutional Review Board (No. 680) and the requirement for written informed consent was waived.
2.2 Methods and equipment

All patients were administered local anesthesia with mild sedation (intravenous administration of midazolam) during the bronchoscopies. Before bronchoscopy, a bronchial route was planned based on the chest CT images. To detect the bronchial route to the target lesions, a virtual bronchoscopic navigation/simulation system (SYNAPSE VINCENT® Fujifilm, Tokyo, Japan) was used. The EB-530T (Fujifilm) and BF-1T260 (Olympus, Tokyo, Japan) bronchoscopes were used along with the PB2020-M (Fujifilm) and UM-S20-17S (Olympus) ultrasound probes. The K-203 (Olympus) GS was used, and 2 pairs of biopsy forceps were inserted into the GS alternately and repeatedly for biopsying lung tissue. An ultrasound probe loaded with a GS was inserted from the working channel end under x-ray fluoroscopy. R-EBUS patterns were obtained on the screen while manipulating the probe when the lesion was localized. The R-EBUS signals on the display were captured and analyzed. After confirming the location of the lesions, the probe was withdrawn while the GS was held in place, and the forceps were placed into the GS for standard transbronchial sampling under fluoroscopic guidance. Numerous specimens were obtained because the GS was fixed and double forceps were used. Moreover, specimens were inflated with a syringe before immersion to formalin liquid.

2.3 CT scan characteristics

CT scans were obtained with various scanners, including the Aquilion ONE, Aquilion CX, and Aquilion 64-section multidetector (Toshiba Medical Systems Corporation, Tochigi, Japan). Scans were obtained with the patient in the supine position at full inspiration. High-resolution CT images were reconstructed with 1.0–2.0 mm collimation and 10–20 mm slice intervals, and ground glass opacity (GGO), consolidation, reticulation, and nodular
patterns were diagnosed based on CT findings [6].

2.4 CT window in the sampled area
The mean CT Hounsfield units (HU) in the sampled area, where lung tissues were biopsied by TBLB, not in all abnormal lesions, was measured in patients with consolidation. The Hounsfield scale of tissue density is based on two values: air, defined as -1000 HU (minimum HU value), and water, defined as 0 HU.

2.5 R-EBUS patterns
The R-EBUS patterns were used to confirm if the probe and GS had reached the lesion. The R-EBUS patterns were defined according to previous reports [4, 7, 8]. Blizzard, which is the whitish acoustic shadow of air-containing lung tissue, and mixed blizzard, which is diffuse heterogeneity with several hyperechoic dots, linear arcs, and vessels, were reported as R-EBUS patterns for peripheral lung nodules [4]. In contrast to the blizzard and mixed blizzard patterns, in the present study, a dense pattern was defined as a darker and more homogeneous signal with irregularly-distributed mottling and linear hyperechoic areas, reflecting dense lung tissue and cellularity. R-EBUS characteristics in association with CT findings and pathological diagnostic yield were evaluated.

2.6 Statistical analysis
Descriptive statistics are presented as frequency, percentage, and median (range). Differences between groups were compared using Student’s t-tests and Fisher’s exact tests (for categorical variables). Data were analyzed using JMP 9 version 9.0.3 (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at p <
Results

3.1 Baseline characteristics

The patient characteristics are shown in Table 1. The cases comprised 35 patients (10 female and 25 male) with a median age of 67 years. Chest CT of the biopsied area showed a reticular pattern in 6, consolidation pattern in 15, GGO pattern in 9, nodular pattern in 2, and no obvious findings in 3 of the 35 patients. Before obtaining lung tissue by bronchoscopy, all patients had suspected DPLD, specifically, IPF, idiopathic nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), unclassified interstitial pneumonia (UCIP) based on the 2013 idiopathic interstitial pneumonias classification \[2\], collagen vascular disease associated with interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis (HP), drug-induced lung disease (DILD), acute eosinophilic pneumonia (AEP), allergic bronchopulmonary aspergillosis (ABPA), or HTLV-1 associated bronchiolo-alveolar disorder (HABA). Various types of CT findings were observed, and the clinico-radiological diagnosis was heterogeneous in these patients.

[Place Table 1 around here]

3.2 Correlation between chest CT findings and R-EBUS patterns

Table 2 shows the correlation between the chest CT findings and R-EBUS patterns. CT findings where R-EBUS and TBLB were performed were evaluated in association with the R-EBUS patterns. All 6 patients with a reticular pattern, 9 with a GGO pattern, and 2 with a nodular pattern in the area of the biopsied lesion on chest CT showed a R-EBUS blizzard pattern. A blizzard pattern was found in 4 patients and a dense pattern in 11 patients with a consolidation pattern. A mixed blizzard pattern was not found in any case.
Representative reticular, GGO, consolidation, and nodular patterns on chest CT and blizzard and dense patterns on R-EBUS are shown in Figures 1 and 2, respectively. The dense pattern was a novel R-EBUS pattern in patients with suspected DPLD and it was only observed in patients with a consolidation pattern. Conversely, the blizzard pattern was observed in patients with all types of CT findings.

[Place Table 2 around here]

3.3 Correlation between R-EBUS patterns and CT values in patients with consolidation patterns

In patients whose chest CT showed consolidation patterns on CT images, two R-EBUS patterns were found; blizzard and dense patterns. The mean CT value of the biopsied area was evaluated (Figure 3); it was significantly higher in patients with a dense pattern than in patients with a blizzard pattern (p < 0.0001; Table 3). There was no significant difference in the evaluation area between the 2 groups (p = 0.5780). In the COP patient with consolidation on CT with a dense pattern on R-EBUS, there was organization in the alveoli and lymphocyte infiltration in the alveoli and alveolar wall and the histopathological density was high (Figure 4). The COP patient with consolidation on CT with a blizzard pattern on R-EBUS had a greater amount of air space in the lung sample in addition to organization and lymphocyte infiltration than had the patient with consolidation and a dense pattern (Figure 5). The difference between dense and blizzard patterns depended on the difference in the radiological and pathological density.

[Place Table 3 around here]

3.4 R-EBUS pattern and its diagnostic value

3.4.1 Pathological diagnostic yield
TBLB was performed based on the R-EBUS patterns with a GS. Compared to patients without R-EBUS signals, the pathological diagnostic yield was significantly higher (> 90%) in patients with overt R-EBUS signals (Table 4). There were 6 patients who could not be diagnosed pathologically because the obtained lung tissue samples were not suitable for pathological diagnosis. Among these 6 patients, chest CT and R-EBUS patterns were available for 3 patients with CHP, UCIP, and sarcoidosis, respectively. The reasons why the obtained lung tissue samples had no diagnostic value were perilobular and perilymphatic distribution of fibrosis and bilateral subpleural slight reticulation, which rendered obtaining sufficient tissue difficult. The remaining 3 sarcoidosis patients without R-EBUS pattern could not be diagnosed using the TBLB specimens because there were no CT findings and the TBLB specimens did not include sufficient lesion matter.

3.4.2 Pathological findings and final diagnosis

R-EBUS patterns, radiological and pathological findings, and final diagnosis are shown in Table 5. Patients with reticular and blizzard patterns were diagnosed with IPF, idiopathic NSIP, UCIP, and DILD (NSIP-like pattern). Patients with GGO and blizzard patterns were diagnosed with idiopathic NSIP, HP, DILD (NSIP and OP-like patterns), or HABA, and polymyositis and dermatomyositis was diagnosed with consideration of the clinical course: the anti-aminoacyl t-RNA antibody was found to be positive after CR diagnosis. Patients with nodular and blizzard patterns were diagnosed with sarcoidosis. Patients with consolidation and blizzard patterns were diagnosed with COP, DILD (OP-like pattern), or sarcoidosis, and patients with consolidation and dense patterns were diagnosed with COP, sarcoidosis, ABPA, or pulmonary infarction. Final diagnosis was reached with consideration of the degree to which the CR and pathological diagnoses agreed.
3.5 Complications

Grade 3 pneumothorax, as assessed by the common terminology criteria for adverse events v4.0, occurred in only 1 case; this patient’s pneumothorax resolved with thoracic drainage without surgery. There were no severe complications.

Discussion

This study investigated the characteristics of R-EBUS patterns in association with CT findings and the mean CT HU in the sampled area, and the pathological diagnosis with TBLB samples obtained with R-EBUS-GS. This study showed the usefulness of associating dense and blizzard R-EBUS patterns with the reticular, consolidation, GGO, and nodular patterns in diagnosing DPLD.

R-EBUS has been widely used to diagnose peripheral pulmonary lesions in suspected lung cancer and has been shown to successfully identify 96% of nodules, with larger nodules associated with better pathological diagnostic yield [9]. The blizzard pattern of R-EBUS was previously reported to be associated with the ground glass nodules of lung cancer [4]. The present study was the first to show a dense R-EBUS pattern in DPLD patients with consolidation because the dense pattern has not been previously evaluated as a R-EBUS pattern. The blizzard pattern was also shown for the first time as a characteristic R-EBUS pattern in DPLD patients with reticular, consolidation, GGO, and multiple small nodular patterns in the present study.

The dense pattern was found only in patients with a consolidation pattern when the R-EBUS probe was most closely related to the most severe lesion; however, the blizzard pattern was also found in the same patients when the R-EBUS probe did not approach the
most severe lesion. Conversely, there were several patients with consolidation who had only a blizzard pattern. It was considered that the R-EBUS patterns differed according to the difference in the density of the consolidation. When the R-EBUS signal showed a dense pattern, the obtained lung tissue samples may have been denser than were those obtained when the signal showed a blizzard pattern, and dense lung samples could be considered to contribute to more precise pathological diagnosis because the most severe lesion on CT could include greater quantities of abnormal lesions. Therefore, before bronchoscopy, it would be preferable to predict whether a dense pattern would be confirmed in patients with consolidation.

In the present study, when the CT value in consolidation was approximately 0 HU, a dense pattern would be expected and a blizzard pattern would not be observed. The mean CT value could help us predict the R-EBUS patterns, and that may conserve procedural time by eliminating the need to search for a dense pattern in patients with blizzard pattern. Assessment of the CT values in the consolidation pattern prior to sampling lung tissue was needed for better evaluation of the R-EBUS patterns and for sampling more suitable tissues during bronchoscopy.

The blizzard pattern was also useful for obtaining lung tissue samples and pathological diagnosis in suspected DPLD patients. In the present study, the pathological diagnostic yield was higher than 90% in patients with dense and blizzard patterns among patients who underwent TBLB with R-EBUS-GS and was significantly higher in patients with dense and blizzard patterns than in patients without R-EBUS patterns. The overall pathological diagnostic yield of TBLB in patients with underlying ILD is approximately 25–75% [10-13]. The pathological diagnostic yield for usual interstitial pneumonia (UIP) can be 30–69% [14, 15] and 12.5–16% for non-UIP [10, 15]. The pathological diagnostic yield of TBLB with R-
EBUS-GS in the present study was higher than that without R-EBUS-GS in the previous study [10-15].

Therefore, positive dense and blizzard R-EBUS signals may contribute toward obtaining suitable tissue samples for pathological evaluation through TBLB when also using a GS in DPLD patients. Evaluating R-EBUS pattern differences was needed for better sampling of lung tissues leading to pathologically-precise diagnosis.

After R-EBUS evaluation, the GS was fixed in the bronchus, and lung tissues were repeatedly obtained by TBLB through the fixed GS. Additionally, just after withdrawal of one pair of forceps, another was immediately inserted into the GS for biopsy alternately and repeatedly. GS and 2 pairs of forceps enabled obtaining more lung tissue to diagnose DPLD. In addition, DPLD lesions were detected three-dimensionally by R-EBUS compared with two-dimensional radiography, and tissue sampling was performed according to the location at which the R-EBUS pattern had the widest and strongest shadow. Consequently, R-EBUS allowed us to accurately evaluate the lesion site of DPLD, and R-EBUS-GS allowed for more precise lung-tissue acquisition.

In the present study, pathological findings and final diagnosis varied, and they did not depend on R-EBUS patterns. Therefore, R-EBUS patterns cannot provide specific clinical DPLD diagnosis and prediction of the effect of treatment.

Grade 3 pneumothorax was observed in only 1 case and it resolved with thoracic drainage without surgery. There was no severe hemorrhage and pneumothorax, suggesting that GS had a hemostatic effect via the bronchial wedge and that confirmation of the precise position by R-EBUS reduced the incidence of pneumothorax.

The study has some limitations; it was a retrospective analysis, performed in a single institute. The dense pattern was observed in only patients with consolidation and in most of OP patients; therefore, the usefulness of the dense pattern is unknown in patients other
than those with OP with consolidation. Comparisons of pathological density between dense and blizzard R-EBUS patterns using a numerical score could not be performed because there were various types of infiltrated cells and organizations, and there were some crush artifacts in the lung tissues. Furthermore, the sample size in this study was small, and the pathological findings were highly heterogeneous. Lack of surgical lung biopsy limited our ability to evaluate the quality and quantity of the TBLB samples obtained using R-EBUS-GS. Prospective trials assessing the utility of R-EBUS for DPLD management are recommended.

There has been growing interest in transbronchial cryobiopsy, an innovative method of obtaining samples from DPLD patients. R-EBUS could be useful for cryobiopsy similar to TBLB, and thus a multicenter, prospective, clinical trial assessing the safety and utility of cryobiopsy with R-EBUS is currently underway in our hospital in collaboration with other institutions.

Conclusions

In conclusion, this was the first report showing the usefulness of the dense and blizzard patterns of R-EBUS in diagnosing DPLD. The positive R-EBUS patterns when also using a GS with TBLB may enable more precise lung-tissue sample acquisition. Therefore, R-EBUS-GS may be a valuable tool to combine with TBLB in diagnosing DPLD.

Abbreviations

ABPA: Allergic bronchopulmonary aspergillosis
AEP: Acute eosinophilic pneumonia
CTCAE: Common terminology criteria for adverse events
COP: Cryptogenic organizing pneumonia
CT: Computed tomography
DILD: Drug-induced lung disease
DPLD: Diffuse parenchymal lung disease
GGO: Ground glass opacity
GS: Guide sheath
HABA: HTLV-1 associated bronchiolo-alveolar disorder
HP: Hypersensitivity pneumonitis
HU: Hounsfield units
ILD: Interstitial lung disease
IP: Interstitial pneumonia
IPF: Idiopathic pulmonary fibrosis
NSIP: Nonspecific interstitial pneumonia
PM/DM: Polymyositis and dermatomyositis
R-EBUS: Radial-endobronchial ultrasonography
TBLB: Transbronchial lung biopsy
UCIP: Unclassified interstitial pneumonia
UIP: Usual interstitial pneumonia

Declarations

**Ethics approval and consent to participate**

This study was approved on June 1, 2018 by the hospital’s Institutional Review Board (No. 680) and the requirement for written informed consent was waived.

**Consent for publication**

Not applicable.

**Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Competing interests
The authors declare that they have no competing interests.

Funding
None.

Authors’ contributions
MI participated in bronchoscopy, the design of the study and the collection, analysis, and interpretation of data; performed the statistical analysis; drafted the manuscript. NK participated in bronchoscopy, the collection, analysis, and interpretation of the radiography images. NA participated in bronchoscopy, the collection, analysis, and interpretation of the radiography images. MT participated in bronchoscopy, the collection, analysis, and interpretation of data. HY participated in bronchoscopy, the collection, and interpretation of data. TJ participated in bronchoscopy, the collection, and interpretation of data. AM participated in the collection, and interpretation of data. YB participated in interpretation of the pathological findings. TK participated in interpretation of the pathological findings. TT participated in interpretation of the pathological findings. TI participated in bronchoscopy, the design of the study and the collection, analysis, and interpretation of data; performed the statistical analysis.

All authors critically reviewed the manuscript in relation to important intellectual content.

References
1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198:e44-68.
2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial
pneumonias. Am J Respir Crit Care Med. 2013;188:733-48.

3. Kurimoto N, Miyazawa T, Okimas S, Maeda A, Oiwa H, Miyazu Y, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest. 2004;126:959-65.

4. Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T. Radial endobronchial ultrasound images for ground-glass opacity pulmonary lesions. Eur Respir J. 2015;45:1661-8.

5. Shinagawa N, Nakano K, Asahina H. Endobronchial ultrasonography with a guide sheath in the diagnosis of benign peripheral diseases. Ann Thorac Surg, 2012;93:951-7.

6. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246:697-722.

7. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012;142:385-93.

8. Herth FJ, Eberhardt R, Becker HD, Ernst A. Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. Chest. 2006;129:147-50.

9. Chen A, Chenna P, Loiselle A, Massoni J, Mayse M, Misselhorn D. Radial probe endobronchial ultrasound for peripheral pulmonary lesions. A 5-year institutional experience. Ann Am Thorac Soc. 2014;11:578-82.

10. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63:v1-58.

11. Descombes E, Gardiol D, Leuenberger P. Transbronchial lung biopsy: an analysis of
530 cases with reference to the number of samples. Monaldi Arch Chest Dis. 1997;52:324-9.

12. MacJannette, R., Fiddes J, Kerr K, Dempsey O. Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? Eur Respir J. 2007;29:1064.

13. Ensminger SA, Prakash UB. Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? Eur Respir J. 2006;28:1081-4.

14. Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, et al. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. Chest. 2017;151:389-99.

15. Tomassetti S, Cavazza A, Colby TV, Ryu JH, Nanni O, Scarpi E, et al. Transbronchial biopsy is useful in predicting UIP pattern. Respir Res. 2012;13:96.

Tables

Table 1. Baseline characteristics of patients with interstitial lung disease
| Age years       | 67 (22-82) |
|-----------------|------------|
| Gender          | 10/25      |
| Male            | 25 (71.4)  |
| Female          | 10 (28.6)  |

| CT findings (biopsied area) |               |
|-----------------------------|---------------|
| Reticular pattern           | 6 (17.1)      |
| Consolidation pattern       | 15 (48.6)     |
| Ground glass opacity pattern| 9 (25.7)      |
| Nodular pattern             | 2 (5.7)       |
| None                        | 3 (8.6)       |

| Clinico-radiological diagnosis |               |
|--------------------------------|---------------|
| IPF                            | 1 (2.9)       |
| Idiopathic NSIP                | 3 (8.6)       |
| COP                            | 9 (25.7)      |
| UCIP                           | 3 (8.6)       |
| Sarcoidosis                    | 7 (20)        |
| HP                             | 3 (8.6)       |
| DILD                           | 6 (17.1)      |
| ABPA                           | 2 (5.7)       |
| HABA                           | 1 (2.9)       |

| Biopsied area                |               |
|------------------------------|---------------|
| Upper                        | 16 (45.7)     |
| Middle or lingula            | 14 (40)       |
| Lower                        | 28 (80)       |

| Cases biopsied in two or more lobes | 17 (48.6) |
| Number of times of biopsy (per patient) | 10 (4-20) |
| Complication (CTCAE v4.0 > grade 3) |         |
| Pneumothorax                  | 1 (2.9)     |
| Hemorrhage                    | 0           |

Data are presented as median (range) or n (%); n = 35. CT: computed tomography; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; COP: cryptogenic organizing pneumonia; UCIP: unclassified interstitial pneumonia; HP: hypersensitivity pneumonitis; DILD: drug-induced interstitial lung disease; ABPA: allergic bronchopulmonary aspergillosis; HABA: HTLV-1 associated bronchiolo-alveolar disorder; CTCAE: common terminology criteria for adverse events.
Table 2. Correlation between chest CT findings and R-EBUS patterns

| CT findings                        | Blizzard | Dense |
|------------------------------------|----------|-------|
| Reticular pattern                  | 6        | 0     |
| Consolidation pattern              | 4        | 11    |
| Ground glass opacity pattern       | 9        | 0     |
| Nodular pattern                    | 2        | 0     |
| None                               | 0        | 0     |

Data are presented as n. CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography

Table 3. Correlation between R-EBUS patterns and CT values in patients with consolidation pattern

| Subjects n | Blizzard | Dense |
|------------|----------|-------|
| Area of CT value (mm²) | 62 (34-189) | 104.5 (43-170) |
| CT value (Hounsfield Units) | -163.7 (-282.5 - -114.7) | 34.0 (-13.8 - 57.9) |

Data are presented as median (range). CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography

Table 4. Pathological diagnostic yield by R-EBUS pattern

| R-EBUS pattern | Diagnostic | Non diagnostic | p-value |
|----------------|------------|----------------|---------|
| (+)             | 29/32 (90.6) | 3/32 (9.4)    | < 0.0001 |
| (-)             | 0/3 (0)     | 3/3 (100)     |         |

Data are presented as the number of positive or negative lesions/total lesions (%). R-EBUS: Radial-endobronchial ultrasonography

Table 5. Correlations among CT, R-EBUS, and histopathology
| CT | R-EBUS | Pathological findings/diagnosis (n) | Final |
|----|--------|------------------------------------|-------|
|    |        | Reticulation                        |       |
|    |        | Blizzard                            |       |
|    |        | perilobular alveolar fibrosis (1)    |       |
|    |        | chronic IP (1)                       |       |
|    |        | chronic IP with fibroblastic foci (1), no definite findings (2) | Idiop |
|    |        | slight inflammation of the alveolar wall and intraalveolar organization (1) | DILD |
|    |        | Consolidation                        |       |
|    |        | Blizzard                            |       |
|    |        | OP (1)                              |       |
|    |        | OP (1), foamy macrophage and slight infiltration of eosinophil and alveolar fibrosis (1) | DILD |
|    |        | non-caseous epithelioid cell granuloma (1) | Sarc |
|    |        | Dense                                |       |
|    |        | OP (7)                              |       |
|    |        | pulmonary hemorrhagic infarction (1) | Pulmon |
|    |        | eosinophilic pneumonia (1)          |       |
|    |        | mucoid impaction (1)                |       |
|    |        | no definite findings (1)            |       |
|    |        | Ground glass opacity                |       |
|    |        | Blizzard                            |       |
|    |        | chronic IP (1)                      |       |
|    |        | NSIP (1)                            | Idiop |
|    |        | HP (3)                              |       |
|    |        | lymphocytic alveolitis and intraalveolar organization with type II pneumocyte hyperplasia (3) | DILD |
|    |        | lymphocytic alveolitis with large atypical lymphocytes (1) | Sarc |
|    |        | Multiple nodules                    |       |
|    |        | Blizzard                            |       |
|    |        | non-caseous epithelioid cell granuloma (2) | Sarc |

n: number; CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography; IP: interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; COP:
cryptogenic organizing pneumonia; UCIP: unclassified interstitial pneumonia; HP: hypersensitivity pneumonitis; DILD: drug-induced lung disease; ABPA: allergic bronchopulmonary aspergillosis; PM/DM: polymyositis and dermatomyositis; HABA: HTLV-1-associated bronchiolo-alveolar disorder.

Figures

Figure 1

Representative chest CT patterns. (A) Chest CT showing a reticular pattern in the bilateral peripheral lungs. (B) Consolidation pattern in the bilateral lungs (C) Ground glass opacity pattern in the bilateral lungs. (D) Nodular pattern in the right middle lobe. Circles show the biopsied area.
Figure 2

Representative R-EBUS patterns. (A) Normal lung. (B) Blizzard pattern: noticeable increase in the intensity and large radius of the whitish acoustic shadow. (C) Dense pattern: dark and homogeneous signals with irregularly-distributed mottling and linear hyperechoic areas. R-EBUS: Radial-endobronchial ultrasonography
Correlation between the R-EBUS pattern and CT value in patients with consolidation patterns. The mean CT value of the biopsied area was evaluated. The mean CT value in the dense pattern was higher than that in the blizzard pattern. CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography
Representative CT scans, R-EBUS patterns, and pathological findings in patients with consolidation and dense patterns. (A) Chest CT showing a consolidation pattern in the bilateral lower lobes, and R-EBUS and biopsied area in the right lower lobe (circle). (B) R-EBUS, showing a dense pattern with dark and homogeneous signals with mottling and linear hyperechoic areas. (C) Biopsy sample, showing organization in the alveoli and lymphocyte infiltration in the alveoli and alveolar wall with pathological high density (x5). (D) High magnification of the sample showing organizing pneumonia with fibrinous exudate (x20). CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography.
Figure 5

Representative CT scans, R-EBUS patterns, and pathological findings in patients with consolidation and blizzard patterns. (A) Chest CT showing a consolidation pattern in the left lower lobe, and R-EBUS and biopsied area in left lower lobe (circle). (B) R-EBUS, showing a blizzard pattern with an increase in the intensity and radius of the whitish acoustic shadow. (C) Biopsy sample, showing organization in the alveoli and lymphocyte infiltration in the alveoli and alveolar wall with pathological low density (x5). (D) High magnification of the sample showing organizing pneumonia (x20). CT: computed tomography; R-EBUS: Radial-endobronchial ultrasonography.