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【 ORIGINAL ARTICLE 】

Efficacy and Safety of Endobronchial Ultrasonography with a Guide-sheath for Acute Pulmonary Lesions in Patients with Haematological Diseases

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Abstract:

Objective Acute pulmonary lesions (APLs), defined as an acute infiltrate or nodular lung field, are a major complication in patients with haematological diseases. Recently, endobronchial ultrasonography with a guide-sheath (EBUS-GS) was established as a useful technique for diagnosing pulmonary lesions. This study aimed to evaluate the efficacy and safety of EBUS-GS for managing APLs in patients with haematological diseases.

Methods Our single-centre, retrospective, observational, single-arm, descriptive study enrolled 22 consecutive adult (>20-year-old) patients with haematological diseases and concomitant APL who underwent EBUS-GS between January 2011 and June 2016 at Kameda Medical Center, Chiba, Japan. The primary endpoint was the contribution of EBUS-GS to clinical decision-making. Secondary endpoints were an adequate tissue collection rate, diagnostic yield, complication rate, and 30-day mortality.

Results The median patient age was 70 years old, and 63.6% were men. Acute myeloid leukaemia was the most frequent underlying disease, accounting for 54.5% of patients. The contribution of EBUS-GS to clinical decision-making was recognised in 11 (50.0%) patients. Adequate tissue collection was achieved in 21 (95.5%) patients. The aetiology of the APL was identified in 9 (40.9%) patients. No complications, including severe haemorrhaging and pneumothorax, were observed in any patients, and the 30-day mortality rate was 0%.

Conclusion EBUS-GS may be a suitable diagnostic option for APL in patients with haematological diseases. Further larger-scale and randomised controlled trials are needed to confirm our results.

Key words: adult, bronchoscopy, haematologic disease, image-guided biopsy, lung disease

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Introduction

Acute pulmonary lesions (APLs), defined as an acute infiltrate or nodular lung field, represent a major complication in patients with haematological diseases. APL has numerous causes, such as fungal infection, bacterial infection, neoplastic infiltration, graft-versus-host disease (GVHD), and drug-induced pneumonia, and is associated with high morbidity and mortality in patients with haematological diseases (1, 2). Since the treatment strategy for APL differs markedly according to the aetiology, several diagnostic procedures are used to investigate the cause, including bronchoalveolar lavage (BAL), a traditional transbronchial biopsy (TBB), a computed tomography (CT)-guided biopsy, and a surgical lung biopsy (SLB) (1-6). However, a definitive diagnosis may not be able to be achieved with less-invasive procedures, such as BAL, as a biopsy specimen cannot be obtained.

A biopsy allows for the distinction between fungal colonisation and fungal invasion and may detect underlying processes, such as bronchiolitis obliterans, drug-induced pneu-

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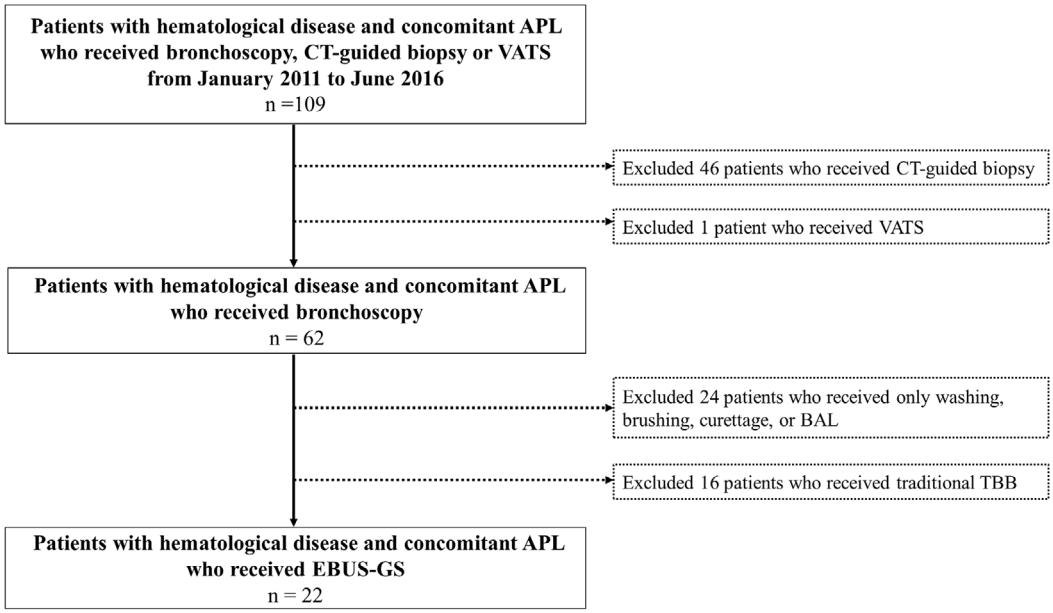

Figure 1. **Patient Selection Flowchart. APL: acute pulmonary lesion, BAL: bronchoalveolar lavage, CT: computed tomography, EBUS-GS: endobronchial ultrasonography with a guide-sheath, TBB: transbronchial biopsy, VATS: video-assisted thoracic surgery**

monitis, and neoplastic lesions. However, a traditional TBB, CT-guided biopsy, and SLB are often avoided in patients with haematological disease due to concerns of serious complications, such as life-threatening haemorrhaging, which can be difficult to manage in patients with haematological diseases owing to their low platelet counts, platelet dysfunction, and impaired blood clotting (7). Thus, safe and less-invasive procedures for obtaining biopsy specimens are indispensable for the management of APL in patients with haematological diseases.

Recently, endobronchial ultrasonography with a guide-sheath (EBUS-GS) has been introduced for the diagnosis of pulmonary lesions, including malignant and non-malignant lesions, such as infections, and is considered to be more effective and safer than traditional TBBs (8). The diagnostic rate of EBUS-GS is reported to be 73.2%, while that of a traditional TBB is 30-60% (9-11).

Given the above, we suspected that EBUS-GS might allow for a high sample collection rate, high diagnostic yield, marked contribution to clinical decision-making, and safe management of APL in patients with haematological diseases. However, little evidence is available regarding EBUS-GS for the diagnosis of APL in this patient population (12). We therefore evaluated the safety and efficacy of EBUS-GS for the diagnosis of APL in patients with haematological diseases in the present study.

Materials and Methods

Study population

Our single-centre, retrospective, observational, single-arm, descriptive study enrolled 22 consecutive adult (>20 years old) patients with haematological diseases and concomitant APL, who underwent EBUS-GS between January 2011 and June 2016 at Kameda Medical Center, Chiba, Japan (Fig. 1). We obtained the information shown in Tables 1-3 from patient records.

The Ethics Committee of Kameda Medical Center approved this study and waived the need to obtain informed patient consent owing to the retrospective, patient-record-based nature of the study.

Identification of APL

All APLs were identified on chest CT when pulmonary abnormalities were suspected clinically, based on symptoms, laboratory data, or chest radiography findings. For the grading of APL distribution, APL was regarded as focal when lesions were present in a single lobe but as multiple when lesions were present in multiple lobes, regardless of the number of lesions. The targeted APLs were classified into 3 categories based on morphology and size: nodules (round lesions with a long diameter <3.0 cm), masses (round lesions with a long diameter ≥3.0 cm), and consolidations (irregular-shape lesions). Furthermore, the distance of the APL from the hilum was defined as previously described (13). Using the area around the hilum on CT as reference, lesions within the inner and middle third ellipses were designated as having a central parenchymal location, whereas lesions in the outer third ellipse were designated as having a peripheral parenchymal location.

Standard protocol of EBUS-GS

Blood coagulation parameters were preprocedurally evaluated, and platelet transfusions were administered before or during the procedure when the platelet count was <50,000/

Table 1. Patient Characteristics.

Parameters	Total (n=22)	Missing
Age (years)	70 (61-74)	0
Male	14 (63.6)	0
Underlying disease		0
Acute myeloid leukaemia	12 (54.5)	0
Acute lymphocytic leukaemia	2 (9.1)	0
Malignant lymphoma	4 (18.2)	0
Multiple myeloma	2 (9.1)	0
Myelodysplastic syndrome	2 (9.1)	0
Allogeneic/autologous transplantation	1 (4.5)	0
Pharmacological treatment before EBUS-GS		
Antibacterial agent	18 (81.8)	0
Antifungal agent	16 (72.7)	0
Pharmacological treatment instituted after appearance of APL and before EBUS-GS	11 (50.0)	0
Respiratory failure (required oxygen)	1 (4.5)	0
Body temperature (°C)	36.8 (36.2-37.4)	0
Laboratory data		
Neutrophil count (/μL)	939 (446-2,574)	0
Haemoglobin (g/dL)	8.7 (7.3-10.8)	0
Platelet count ($\times 10^4$/μL)	12.0 (7.5-23.6)	0
Positive galactomannan antigen (≥0.5)	2 (9.1)	0
CT findings		
Distribution of the acute pulmonary lesion		0
Focal	11 (50.0)	0
Multi	11 (50.0)	0
Type of the target lesion		0
Nodule	12 (54.5)	0
Mass	4 (18.2)	0
Consolidation	6 (27.2)	0
Location		
Central parenchymal location	6 (27.3)	0
Peripheral parenchymal location	16 (72.7)	0
Diameter of the target lesion		
Long diameter (mm)	29.2 (25.7-54.9)	0
Short diameter (mm)	22.1 (18.1-33.1)	0
Bronchus sign		
Positive	20 (90.9)	0
Negative	2 (9.1)	0

Categorical variables are shown as number (%), and continuous variables are shown as median (25-75th percentile). APL: acute pulmonary lesion, CT: computed tomography

μL, as previously described (1). EBUS-GS was not performed when the international normalised ratio of prothrombin time was ≥1.3 or the activated partial thromboplastin time was >1.1 times that of the control.

We followed the standard EBUS-GS protocol (8). In brief, we selected 2 types of video-bronchoscope (BF TYPE 1T-260; 5.9-mm outer diameter, 2.8-mm working channel diameter, or BF TYPE P260F; 4.0-mm outer diameter, 2.0-mm working channel diameter; both Olympus Medical Systems, Tokyo, Japan). Both types were used with a radial EBUS probe (UM-S20-17S; Olympus Medical Systems). The BF 1T-260 was used with a large guide-sheath kit (K-203: large size GS, 2.55-mm diameter; Olympus Medical Systems) mainly for large target lesions (long diameter >30 mm) or small target lesions (long diameter ≤ 30 mm) with a central parenchymal location. The BF P260F was used with a small guide-sheath kit (K-201: small size GS, 1.95 mm in diameter) mainly for small target lesions (long diameter ≤30 mm) with a peripheral parenchymal location. When multiple lesions were found, the lesion with an apparent bronchus sign (a finding on the cross-section of a bronchus, leading directly to or contained within the nodule or mass) was selected as the target lesion for EBUS-GS, as this sign is a predictor of the success of EBUS-GS (14). The bronchial route for the target lesion was planned by reviewing the chest CT images before EBUS-GS. Virtual bronchoscopic

Table 2. Procedure Records of EBUS-GS.

	Total (n=22)	Missing
Combined with virtual bronchoscopy	19 (86.4)	0
Combined with BAL	2 (9.1)	0
Bronchoscopy and guide-sheath		
1T260 (with a large guide-sheath, K203)	9 (40.9)	0
P260 (with a small guide-sheath, K201)	13 (59.1)	0
Location of the target lesion		
Right upper lobe	5 (22.7)	0
Right middle lobe	1 (4.5)	0
Right lower lobe	7 (31.8)	0
Left upper lobe	5 (22.7)	0
Left lower lobe	4 (18.2)	0
EBUS image		
Within	18 (81.8)	0
Adjacent to	4 (18.2)	0
Invisible	0 (0)	0
Numbers of samples obtained	5 (4-5)	1
Total examination time (min)	26 (22-30)	0

Categorical variables are shown as number (%), and continuous variables are shown as median (25-75th percentile). BAL: bronchoalveolar lavage, EBUS: endobronchial ultrasonography, EBUS-GS: endobronchial ultrasonography with a guide-sheath

navigation (LungPoint, Broncus, Mountain View, USA; or Ziostation2, Ziosoft, Tokyo, Japan) guidance was employed in most of these procedures, at the discretion of the attending pulmonologists (15).

Patients received pharyngeal anaesthesia with 8 mL of 2% lidocaine and sedation with intravenous administration of midazolam (1-2 mg) and pethidine (17.5-35 mg). After inserting the bronchoscope into the patient's respiratory tract, 10-15 mL of 2% lidocaine was distributed appropriately. The bronchoscope tip was advanced as near the target lesion as possible under direct vision, and then a radial EBUS probe covered with a guide-sheath was inserted via the working channel of the bronchoscope to the bronchus leading to the target lesion under fluoroscopic guidance (Versi FLEX; Hitachi, Tokyo, Japan). EBUS images before transbronchial sampling were categorised as previously reported: 1) within (the probe was located in the bronchus, inside the target lesion); 2) adjacent to (the probe was located in the bronchus, adjacent to the target lesion); and 3) invisible (the probe was unable to reach the target lesion) (16). We attempted to obtain "within" EBUS images for all image categories of APLs (e.g., nodule and consolidation). After localising the lesion by EBUS, the probe was removed while the guide-sheath was kept in place for subsequent sampling by bronchial brush and biopsy forceps under fluoroscopic guidance. We attempted to obtain at least 5 biopsy specimens using biopsy forceps, since ≥5 biopsy specimens provided the maximum diagnostic yield (≥95%) in a previous study (17). Biopsy specimens were placed into a formalin-water solution and subsequently analysed histologically. In addition, the forceps and brush were rinsed in a tube containing 2 mL of normal saline, which was subsequently used for cytology and bacterial, fungal, and mycobacterial culturing. After collecting adequate samples, the guide-sheath was left in place for two minutes for haemostasis before it was removed.

We typically did not perform BAL, as we prioritised obtaining adequate biopsy specimens within the limited procedure time. When BAL was performed simultaneously (using three 50-ml aliquots of normal saline) with the EBUS-GS procedure, the BAL fluid was submitted for cytology and bacterial, fungal, and mycobacterial culturing.

Diagnostic criteria

Bacterial and mycobacterial infections were diagnosed when a causative organism was identified from EBUS-GS specimen cultures. We used potato dextrose agar for fungal detection, with an incubation temperature of 35°C. The diagnosis of a fungal infection was defined as proven invasive fungal disease, based on the Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group (18). Definitive diagnoses of non-infectious aetiologies, including organising pneumonia and GVHD, were made based on the histological findings of EBUS-GS specimens (19) and clinical information obtained by the attending physician.

Endpoints and statistical analyses

The primary endpoint was the contribution of EBUS-GS to clinical decision-making. EBUS-GS was considered to have contributed to decision-making if the histological or culture finding of EBUS-GS biopsy specimens contributed

Table 3. Outcome Data.

	Total (n=22)	Missing
Primary endpoints		
Contribution to clinical decision-making	11 (50.0)	0
Administration of steroid for OP or GVHD	5 (22.7)	0
Administration of antibacterial agent for bacterial infection	2 (9.1)	0
Avoidance of antifungal agent based on the absence of causative fungus	1 (4.5)	0
Continuation of antifungal agent for fungal disease	1 (4.5)	0
Observation based on the diagnosis of OP with stable status	1 (4.5)	0
Observation based on the exclusion of malignancy and infection	1 (4.5)	0
Secondary endpoints		
Adequate tissue collection		
Yes	21 (95.5)	0
No	1 (4.5)	0
Diagnostic yield		
Identified	9 (40.9)	0
Bacterial infection	2 (9.1)	0
Pseudomonas aeruginosa	1 (4.5)	0
Haemophilus influenzae	1 (4.5)	0
Mycobacterium	0 (0)	0
Fungal disease	1 (4.5)	0
Zygomycosis	1 (4.5)	0
OP	4 (18.2)	0
GVHD	2 (9.1)	0
Not identified	13 (59.1)	0
No adequate tissue	1 (4.5)	0
Complications		
Total	0 (0)	0
Pulmonary haemorrhage	0 (0)	0
Pneumothorax	0 (0)	0
Pulmonary infection	0 (0)	0
Respiratory failure	0 (0)	0
30-days mortality	0 (0)	0

Categorical variables are shown as number (%), and continuous variables are shown as median (25-75th percentile).
OP: organising pneumonia, GVHD: graft-versus-host disease

to clinical decisions, such as whether to use or stop using antibiotics or steroid for the APL. The contributions were assessed based on a medical records review. Secondary endpoints were the adequate tissue collection rate, diagnostic yield, complication rate, and 30-day mortality. When the amount of tissue was sufficient for a pathological assessment, tissue collection was regarded as adequate. Diagnoses were categorised as "identified" (specific aetiology of APL was detected), "not identified" (benign histological findings were detected, although the specific aetiology of APL was not detected, which is clinically useful for excluding malignancy), and "inadequate tissue" (adequate tissue was not obtained). A major complication was defined as a necessitated premature procedure termination or symptomatic postprocedural sequelae, including pneumothorax, significant haemorrhaging (blood loss >100 mL or the need for blood transfusion), infections, air embolism, or other untoward life-threatening outcomes (20).

Categorical variables are shown as percentages, and continuous variables are shown as median (25-75th percentile). As this study aimed to provide epidemiological data using EBUS-GS in patients with haematological diseases and APL, we reported only descriptive statistics. Statistics were obtained using the R software program (version 3.2.3, R Development Core Team; https://www.r-project.org/).

Results

Table 1 shows the patient characteristics. The median age was 70 years old, and 63.6% of patients were men. Acute myeloid leukaemia was the most frequent underlying disease. Before EBUS-GS, 81.8% and 72.7% of patients had received antibacterial and antifungal agents, respectively. Antibacterial or antifungal agents were initiated after the appearance of APL and before EBUS-GS in 50.0% of patients. In these patients, the median period from the start of antimicrobial agents to EBUS-GS was 7 (4-8) days. The median neutrophil count was 939/μL, and the median platelet count was 12.0×10^4/μL. Most target lesions were nodules, and the median long diameter of lesions was 29.2 mm. The bronchus sign was frequently observed.

Table 2 shows procedural records. Virtual bronchoscopy

was combined with EBUS-GS in 86.4% of patients. The right lower lobe was the most frequently biopsied. Overall, 81.8% and 18.2% EBUS-GS images were within and adjacent to images, respectively. The median number of biopsy samples obtained was 5, and the median total examination time was 26 minutes.

Primary and secondary endpoint data are shown in Table 3. EBUS-GS contributed to clinical decision-making in 50.0% of patients. The most frequent clinical action resulting from EBUS-GS findings was administration of steroid, for organising pneumonia (three patients) and GVHD (two patients). Adequate tissue collection was achieved in most patients. APL aetiology was identified in 40.9% of patients and included fungal disease, bacterial infection, organising pneumonia, and GVHD. Regarding the EBUS image, diagnostic yields (percentages of cases with a specific aetiology identified) were 55.6% (10/18) and 25.0% (1/4) in patients with "within" and "adjacent to" images, respectively. Tissue collection was adequate in most patients; nevertheless, the aetiology remained unidentified in 54.5% of patients. No complications occurred, and no patients died within 30 days.

Table 4 shows the detailed characteristics of the 22 patients included in this study. Two patients (patients 17 and 21) received no antibacterial or antifungal drugs, and one was diagnosed with lung abscess (Patient 21). In two cases (patients 6 and 17), the procedure contributed to the clinical decision-making process despite not yielding a final diagnosis. In patient 6, while invasive pulmonary aspergillosis and bacterial pneumonia were listed as suspected diagnoses, the APL in this patient was interpreted as a resolving bacterial pneumonia with a good response to treatment because no fungus was detected in the results of EBUS-GS. Therefore, the administration of antifungal drugs was avoided, and the lesions responded well to continuing antibacterial drugs (aztreonam and vancomycin). Patient 17 presented with multiple nodules on chest CT; pulmonary infiltration by diffuse large B-cell lymphoma and bacterial pneumonia were considered as differential diagnoses. Since EBUS-GS evidenced no signs of malignant infiltration (including those of diffuse large B-cell lymphoma) and no microorganisms, the attending physician decided to follow the APL. A representative case of APL that underwent EBUS-GS is presented in Fig. 2.

Discussion

We retrospectively summarised our experience of 22 patients with haematological diseases who underwent EBUS-GS for diagnosing APL in order to assess the clinical utility and safety of the procedure in such patients. EBUS-GS contributed to clinical decision-making in half these patients, and a specific aetiology was identified in 40.9% of patients, without any complications. Our results provide haematologists and bronchoscopists with new insights into diagnostic strategies for APL in patients with haematological diseases (12).

The diagnosis of APL in patients with haematological diseases is challenging, as a variety of infectious and non-infectious diseases should be considered in the differential diagnosis. Thus, a conventional TBB or CT-guided biopsy has been preferentially used to obtain material for the tissue-based diagnosis (2, 21). This can result in significant haemorrhaging, which can lead to death of patients with haematological disease. In a previous retrospective study of 71 patients with pulmonary infiltrates after bone-marrow transplantation, 19 (27%) complications occurred, including bleeding in 8 (11%) and death in 2 (3%) patients (22). In another study of 67 patients with haematologic malignancies who underwent CT-guided biopsy, bleeding occurred in 6 (8%) patients, and death occurred in 1 patient with abnormal haematologic parameters (5).

EBUS-GS has been reported to be an effective and safe diagnostic modality, yielding a diagnostic rate higher than that of a traditional TBB (9-11) and a 0% severe haemorrhaging rate, as wedging the guide-sheath in the target bronchus helps stop bleeding during TBBs in EBUS-GS (11, 12, 23, 24). In addition, the procedure allows for the precise localisation and sampling of pulmonary lesions, which may lead to changes in clinical decisions. As little evidence is available regarding the efficacy and safety of EBUS-GS for diagnosing APL in patients with haematological diseases, we conducted this relatively large retrospective cohort study (12).

The diagnostic yield of EBUS-GS is higher than that of a conventional TBB (11). A meta-analysis reported a pooled diagnostic yield of 73.2% in EBUS-GS. The procedure enables the confirmation of the lesion location and repeated procurement of tissue samples from the same position (11). Several factors, such as lesion size, bronchus sign, and EBUS probe position, affect the diagnostic yield of EBUS-GS (11, 14, 17, 23). In a large meta-analysis, the diagnostic yield of guided bronchoscopy decreased with lesion size (≤ 20 mm) (11). In addition, the CT bronchus sign was also reported to be a significant predictor of a successful bronchoscopic diagnosis (14). Furthermore, positioning the probe within the lesions on the EBUS image produced an increased diagnostic yield (17). In the present study, adequate tissue collection was achieved in 21 (95.5%) patients; the mean long diameter of the target lesion was 29.2 mm, 20 (90.9%) of patients had a bronchus sign, and "within" EBUS images were obtained for 18 (81.8%) patients. However, the diagnostic yield was 40.9%, almost half of the adequate tissue collection rate. The final diagnoses were bacterial infection, fungal disease, and organising pneumonia.

In previous studies, the diagnostic yield of bronchoscopy using EBUS in benign disease was reported to be relatively low (29-69%), partly because the diagnostic criteria for benign disease are difficult to define (19). In addition, the initiation of antimicrobials before the procedure may have decreased the diagnostic yield of pulmonary infectious disease (25). In our study, antibacterial and antifungal agents were administered to 81.8% (18 patients) and 72.7% (16 pa-

Table 4. **Detailed Data of 22 Patients with Haematological Diseases and Concomitant Acute Pulmonary Lesions who Underwent EBUS-GS.**

Patient	Age	Sex	Initial presentation	Underlying disease and treatment	Antimicrobial agents		New antimicrobial treatment for APL before BS	EBUS image type	Diagnoses considered by the attending physician before BS	Results of BS				Final diagnosis according to BS	Contribution to clinical decision-making
					Before appearance of APL	After appearance of APL				Number of samples obtained via biopsy	Results of BAL	Results of EBUS-GS			
												Microbiological findings	Pathological findings		
1	71	M	Fever for 2 days and multiple nodules on chest CT	IDR and Ara-C for AML	FLCZ, CFPM	FLCZ, CFPM	-	Within	IPA, zygomycosis bacterial pneumonia	3	-	Negative	No adequate tissue	No adequate tissue	No
2	67	F	New focal nodule on chest CT	Azacitidine for AML	CFPM, VRCZ	CFPM, VRCZ	-	Within	Zygomycosis, bacterial pneumonia	4	-	Negative	Fibrin deposition	Not identified	No
3	74	M	Fever for 3 days and focal nodule on chest CT	GEM, CBDCA, and DEX for DLBCL	ITCZ	ITCZ, CFPM	CFPM for 3 days	Within	IPA, zygomycosis, bacterial pneumonia	6	-	Pseudomonas aeruginosa	Fibrinous exudate	Bacterial infection	Yes (administration of antibacterial agent for bacterial pneumonia)
4	75	M	Fever for 16 days and focal consolidation on chest CT	Azacitidine for MDS	ITCZ, CFPM	ITCZ, CFPM	-	Within	IPA, bacterial pneumonia, OP	6	-	Negative	OP	OP associated with MDS	Yes (administration of steroids)
5	71	M	Increase in the size and number of multiple nodules on chest CT	ETP and Ara-C for AML	TAZ/PIPC	TAZ/ PIPC, VRCZ, LZD	VRCZ, LZD for 3 days	Adjacent to	IPA, zygomycosis, bacterial pneumonia	4	-	Negative	Lipid pneumonia	Not identified	No
6	71	M	Fever and focal mass on chest CT	Azacitidine for AML	FLCZ, AZT, VCM	FLCZ, AZT, VCM	-	Within	IPA, bacterial pneumonia, OP	5	-	Negative	Bronchitis	Not identified	Yes (avoidance of additional antifungal agent based on the absence of causative fungus)
7	66	F	Fever for 3 days and multiple nodules on chest CT	Desatinib for ALL	TAZ/PIPC	TAZ/PIPC	-	Within	IPA, zygomycosis, bacterial pneumonia	4	-	Negative	Fibrosis	Not identified	No
8	82	M	Increase in size of focal nodule on chest CT and high serum GM antigen (1.2)	MTX and leucovorin for DLBCL	FLCZ, CTRX	FLCZ, CTRX	-	Within	IPA, bacterial pneumonia	3	-	Negative	Mild inflammation and fibrosis	Not identified	No
9	78	F	Fever for 3 days and focal nodule on chest CT	IDR and ACR for AML	ST, ITCZ	CFPM, MCFG	CFPM, MCFG for 4 days	Within	IPA, zygomycosis, bacterial pneumonia	5	-	Negative	Lung tissue with haemorrhage and fibrin deposition	Not identified	No
10	35	M	Increase in the size and number of multiple nodules on chest CT	IDR and Ara-C for AML	TAZ/ PIPC, VCM	TAZ/ PIPC, VCM, VRCZ	VRCZ for 9 days	Adjacent to	IPA, zygomycosis, septic emboli	4	-	Negative	Fibrosis	Not identified	No
11	60	M	New multiple nodules on chest CT	IDR and Ara-C for AML	TAZ/PIPC	TAZ/PIPC L-AMB	L-AMB for 7 days	Within	IPA, zygomycosis, bacterial pneumonia, OP, lung infiltration of AML	6	-	Negative	OP	Not identified	No

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Table 4. Detailed Data of 22 Patients with Haematological Diseases and Concomitant Acute Pulmonary Lesions who Underwent EBUS-GS. (Continued)

Patient	Age	Sex	Initial presentation	Underlying disease and treatment	Antimicrobial agents		New antimicrobial treatment for APL before BS	EBUS image type	Diagnoses considered by the attending physician before BS	Results of BS				Final diagnosis according to BS	Contribution to clinical decision-making
					Before appearance of APL	After appearance of APL				Number of samples obtained via biopsy	Results of BAL	Results of EBUS-GS			
												Microbiological findings	Pathological findings		
12	18	M	New multiple consolidations on chest CT	Dasatinib for ALL after allo-BMT	CTRX	CTRX	-	Within	GVHD, PAP DILD	6	Increase in lymphocytes, and no microbial detection	Negative	OP	GVHD	Yes (administration of steroids)
13	75	M	Fever for 2 days and multiple masses on chest CT	Azacitidine for MDS	FLCZ	FLCZ	-	Within	Bacterial pneumonia, IPA, OP	7	-	Negative	OP	OP associated with MDS	Yes (administration of steroids)
14	62	F	Fever for 20 days and focal mass on chest CT	IDR and Ara-C for AML	MEPM	MEPM, VRCZ, VCM	VRCZ and VCM for 7 days	Within	IPA, bacterial pneumonia, Tb	5	-	Negative	OP	Not identified	No (after BS, CT-guided biopsy revealed IPA)
15	44	M	Fever for 2 days and focal consolidation on chest CT	IDR for AMMoL	FLCZ AZT, MNZ	FLCZ, AZT, MNZ, L-AMB	L-AMB for 4 days	Within	Zygomycosis, IPA, bacterial pneumonia	5	-	Negative	Fibrotic lung tissue	Not identified	No
16	47	M	Fever for 7 days and focal mass on chest CT	Post allo-BMT for DLBCL	-	VRCZ, CTRX	VRCZ and CTRX for 7 days	Within	Bacterial pneumonia, GVHD, IPA	5	-	Negative	OP	GVHD	Yes (administration of steroids for OP)
17	79	F	New multiple nodules on chest CT	Observation for MTX-related DLBCL	-	-	-	Within	Lung infiltration by DLBCL, bacterial pneumonia	3	-	Negative	Inflammatory change	Not identified	Yes (observation based on the exclusion of malignancy and bacterial infection)
18	67	F	New multiple nodules on chest CT	R-CHOP for DLBCL	FLCZ, acyclovir	FLCZ, acyclovir, CFPM	CFPM for 14 days	Adjacent to	Tb, NTM, DILD	5	Increase of lymphocites, no microbial detection	Negative	OP	COP	Yes (observation based on the diagnosis of OP with a stable status)
19	69	F	Fever for 7 days and focal nodule on chest CT	AML before treatment	-	SBT/ ABPC	SBT/ ABPC for 7 days	Within	OP, bacterial pneumonia, IPA	Unknown	-	Negative	OP	OP associated with AML	Yes (administration of steroids for OP)
20	71	M	New multiple consolidations on chest CT	Azacitidine for MDS	TAZ/PIPC	TAZ/ PIPC, L-AMB	L-AMB for 35 days	Within	IPA, zygomycosis, bacterial pneumonia, OP	5	-	Negative	Zygomycosis	Zygomycosis	Yes (continuation of antifungal agents for fungal disease)
21	59	F	Fever and cough for 14 days and multiple nodules on chest CT	Rituximab, bendamustine	-	-	-	Within	IPA, zygomycosis, bacterial pneumonia, OP	9	-	Haemophilus influenzae	Lung abscess	Lung abscess	Yes (administration of antibacterial agent for bacterial infection)
22	73	M	Increase in focal nodule on chest CT	R-CHOP for DLBCL	-	-	-	Adjacent to	Tb, bacterial pneumonia	5	-	Negative	Inflammatory granulation tissue	Not identified	No

ACR: aclarubicin, ALL: acute lymphocytic leukaemia, Allo-BMT: allogeneic bone marrow transplantation, AMMoL: acute myelomonocytic leukaemia, AML: myeloid leukaemia, APL: acute pulmonary lesion, Ara-C: cytarabine, AZT: aztreonam, BAL: bronchoalveolar lavage, BS: bronchoscopy, CBDCA: carboplatin, CFPM: cefepime, COP: cryptogenic organizing pneumonia, CT: computed tomography, CTRX: ceftriaxone, DEX: dexamethasone, DILD: drug-induced lung disease, DLBCL: diffuse large B-cell lymphoma, EBUS: endobronchial ultrasonography, EBUS-GS: endobronchial ultrasonography with a guide-sheath, ETP: etoposide, FLCZ: fluconazole, GEM: gemcitabine, GM: galactomannan, GVHD: graft-versus-host disease, IDR: idarubicin, INH: isoniazid, IPA: invasive pulmonary aspergillosis, ITCZ: itraconazole, L-AMB: liposomal amphotericin B, LZD: linezolid, MCFG: micafungin, MDS: myelodysplastic syndromes, MEPM: meropenem, MTX: methotrexate, MNZ: metronidazole, OP: organising pneumonia, PAP: pulmonary alveolar proteinosis, R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, and prednisolone, RFP: rifampicin, SBT/ABPC: sulbactam/ampicillin, ST: sulfamethoxazole-trimethoprim, TAZ/PIPC: tazobactam/piperacillin, Tb: tuberculosis, VCM: vancomycin, VRCZ: voriconazole

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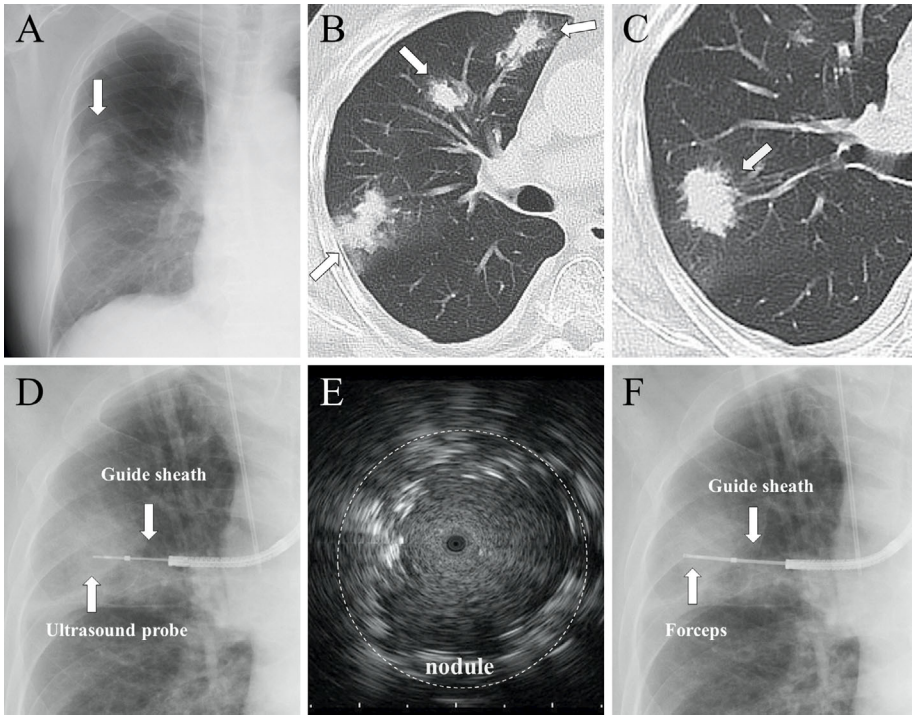

Figure 2. Representative Case. A 74-year-old man with diffuse large B-cell lymphoma developed febrile neutropenia and APL during chemotherapy. Chest radiography showing pulmonary infiltrates in the middle part of the right lung field (A) and chest computed tomography showing multiple pulmonary nodules in the right upper lobe (B). The largest nodule, measuring 25.7 mm in the long diameter, in the right S^2b, with a positive bronchus sign (C), was selected as the target lesion. During the EBUS-GS procedure, a radial probe covered by the guide-sheath was introduced into the right B^2b (D). EBUS showed a low-echoic nodule surrounded by a highly reflective interface between the aerated lung and the lesion, indicating a "within" EBUS image (E). Biopsy forceps were introduced through the guide-sheath, and six specimens were obtained (F). Finally, the APL was diagnosed as bacterial pneumonia caused by *Pseudomonas aeruginosa* based on the result of culturing. APL: acute pulmonary lesion, EBUS-GS: endobronchial ultrasonography with a guide-sheath

tients), respectively, which may have contributed to the low diagnostic yield. As shown in Table 4, histopathological findings, such as inflammation, fibrosis, fibrin deposition, and inflammatory granulation, were observed even in patients in whom a final diagnosis could not be identified. These nonspecific pathological diagnoses may have been reflective of respiratory infections, such as bacterial pneumonia and pulmonary mycosis, that were obscured by previous treatment with antibacterial and antifungal agents. Nevertheless, EBUS-GS contributed to clinical decision-making in half our patients, leading to the administration, termination, or maintenance of treatment drugs.

Haemorrhaging is a major complication after a traditional TBB, although rare (0.73-2.8%) (20, 26, 27). Patients with haematological disease are at high risk of severe haemorrhaging after TBB owing to low platelet counts and coagulation abnormalities (22). In contrast, the safety of EBUS-GS for peripheral pulmonary lesions has been established, and significant haemorrhaging has not been reported in previous studies (11, 24). In a systematic review, no patients in any study experienced bleeding requiring intervention (23).

Pneumothorax is another major complication after a TBB and CT-guided biopsy. The pneumothorax rate after EBUS-GS (0-5.1%) is lower than that after a CT-guided biopsy (20-38.5%) (2, 5, 23, 24). A previous study assessing the efficacy of R-EBUS in haematological patients observed no complications (12), similar to our study.

Several limitations associated with the present study warrant mention. First, this was a single-centre, retrospective, observational study. Although the number of patients enrolled was the highest to date, the sample size was still small. Second, this study was prone to selection bias. As shown in Fig. 1, 22 of the 109 patients with haematological diseases and concomitant APL underwent EBUS-GS; many others were diagnosed using a CT-guided biopsy or traditional TBB. A CT-guided biopsy was preferentially selected for patients with peripheral APLs with a negative bronchus sign. In turn, a traditional TBB was performed mainly in patients requiring a biopsy between January 2011 and April 2012, the period in which the transition from a traditional TBB to EBUS-GS occurred in our institution. However, as shown in Table 1, almost half of the APLs were categorised as nodules <3 cm in size, suggesting that EBUS-GS contributed to a high tissue collection rate. Consequently, our find-

ings must be interpreted with caution.

However, our findings have important implications for clinical practice. APL in haematological disease is difficult to diagnose, but identifying the aetiology of the APL is crucial for appropriate treatment. EBUS-GS yields a high sample collection rate, contributes to clinical decision-making, and is safe. Further prospective studies are therefore warranted.

Conclusion

EBUS-GS for APL in patients with haematological diseases contributed to clinical decision-making in 50.0% of patients, without any complications. Thus, EBUS-GS may be a viable diagnostic option for APL in patients with haematological diseases. Further larger-scale and randomised controlled trials are needed to confirm our results.

The authors state that they have no Conflict of Interest (COI).

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