Diagnostic yield of fiber optic bronchoscopy in alveolar and/or ground glass opacification in chest computed tomographic scan

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Background and objective Transbronchial lung biopsy (TBLB) can be obtained using forceps and usually represents the centrilobular regions. Therefore, disorders that are centered around terminal and respiratory bronchioles or distributed along the lymphatic routes can be diagnosed. This study investigated the diagnostic yield of flexible bronchoscopy in patients with ground-glass opacity (GGO) or alveolar filling for histopathological diagnosis and found out its complications.

Patients and methods Twenty-six patients with predominant GGO or alveolar opacity in the chest computed tomographic (CT) scan were submitted for TBLB for histopathological confirmation. Patients with respiratory failure, heart failure, coagulopathy, or pathognomonic CT patterns were excluded. All patients were subjected to full history taking, chest CT scan, and TBLB with histopathological examination of the specimens.

Results The diagnostic yield of TBLB was 73.1%. Histopathological diagnoses included hypersensitivity pneumonitis (23.1%), sarcoidosis (19.2%), adenocarcinoma (11.5%), small cell lung cancer (7.7%), alveolar proteinosis (3.8%), alveolar hemorrhage (3.8%), organizing pneumonia (3.8%), and chronic nonspecific inflammation (26.9%). There was no significant correlation between age, sex, smoking, and histopathological diagnoses. Regarding the predominant CT finding, 15 (57.7%) patients had GGO, whereas 11 (42.3%) patients had alveolar filling with significant (P=0.008) positive correlation between the CT predominant pattern and histopathological diagnoses. There was a positive significant correlation between lymph node enlargement in CT and histopathological diagnosis (P=0.029). Complications from TBLB included the pneumothorax (15.4%) and bleeding (7.7%).

Conclusions TBLB seems to be a useful and safe procedure. It is of a high diagnostic value. Therefore, it could be considered a routine diagnostic procedure before thoracoscopic or open lung biopsy.
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Introduction

High-resolution computed tomography (HRCT) defines ground glass as hazy attenuation of the lung parenchyma that does not obscure the underlying bronchial structures or pulmonary vessels [1].

Predominant ground-glass opacity (GGO) with a diffuse or patchy distribution includes (a) acute disease without fibrosis, for example, pulmonary edema and pulmonary hemorrhage[2]; (b) subacute-chronic disease without fibrosis, for example, alveolar proteinosis and sarcoidosis[3]; (c) acute disease with fibrosis, for example, acute respiratory distress syndrome (ARDS)[4]; and (d) subacute, chronic disease with fibrosis, for example, some idiopathic interstitial pneumonia (IIPs) (respiratory bronchiolitis, desquamative interstitial pneumonia, and cryptogenic organizing pneumonia) [5].

Predominant GGO with a nodular distribution includes (a) nodular with a homogeneous distribution, for example, hypersensitivity pneumonitis and respiratory bronchiolitis [6]. (b) Nodular without homogeneous distribution, for example, pulmonary edema and pulmonary hemorrhage [7].

Alveolar filling: a group of lung disorders that mainly affect the alveoli. There are acute alveolar lung diseases such as pulmonary edema, pneumonia, and alveolar hemorrhage. In addition, there are chronic alveolar lung diseases such as pulmonary alveolar proteinosis and alveolar cell carcinoma [8].

Patients and methods

This prospective interventional study was conducted at the Chest Department, Cairo University Hospitals and the National Institute of Allergy and Chest Diseases. A written informed consent was obtained from all participating patients. Twenty-six patients were included in the study in the period from June 2016

to February 2017. Patients with predominant GGO or alveolar filling in the chest computed tomographic (CT) scan were submitted for transbronchial lung biopsy (TBLB) for histopathological confirmation of the diagnosis. Patients with respiratory failure, heart failure, coagulopathy, or other CT pathognomonic patterns, for example, usual interstitial pneumonia (UIP), lymphangioleiomyomatosis (LAM), and pulmonary Langerhans cell histiocytosis (PLCH) were excluded. The Human Study Committee of the Kasr El-Aini Hospital of Cairo University approved this study.

All patients were subjected to:

(1) Full history taking, including age, sex, residence, hemoptysis, systemic diseases, and drug use.
(2) Chest CT scan (Siemens Somatom Spirit, Siemens Healthcare GmbH, Henkestr. 127, 91052, Erlangen, Germany).
(3) Fiber-optic bronchoscopy and TBLB using Pentax EB-1970TK video bronchoscope, Tokyo, Japan with a 3.2-mm working-channel diameter and 60-cm working length.

Patient preparation before bronchoscopy included intramuscular injection of atropine [9] and oxygen supply through the nasal cannula with monitoring of oxygen saturation using pulse oximetry [10]. Lidocaine 2% was used as local anesthesia (4–5 mg/kg). It offers a relatively wide margin of safety with a rapid onset of action.

The insertion of a bronchoscope may be through the nasal route or oral route. A complete endobronchial inspection was carried out. The choice of the TBLB site depends on radiological findings. We prefer to perform the biopsy from the dependent parts of the lungs. In an event of bleeding, the blood is at least contained in this area before spilling into the other lobes [11].

Once the biopsy site is chosen, the distal end of the bronchoscope is wedged into the specific segmental bronchus. The assistant is asked to introduce and advance the forceps through the working channel of the bronchoscope, gently advance the biopsy forceps through the distal end, and push the biopsy forceps a few centimeters beyond the distal end of the bronchoscope to reach into the desired subsegmental bronchus [11].

Chest radiographs were performed in patients with chest pain or unexplained hypoxia to rule out the pneumothorax [12]. To control procedural bleeding, the bronchoscope is wedged [13] into the appropriate segmental bronchus, and blood is continuously suctioned to avoid contamination. Other options included the administration of iced saline or 20 ml of 1 : 20 000 epinephrine [14].

Three to five biopsies were obtained for every case, fixed in alcohol 95%, stained with hematoxylin and eosin, and then examined microscopically.

Statistical analysis

Data were statistically described in terms of mean±SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Kruskal–Wallis test. For comparing categorical data, the χ^2 test was performed. An exact test was used instead when the expected frequency was less than 5. P values less than 0.05 were considered as statistically significant. All statistical calculations were made using the computer program IBM statistical package for the social science (IBM Corp., Armonk, New York, USA) release 22 for Microsoft Windows.
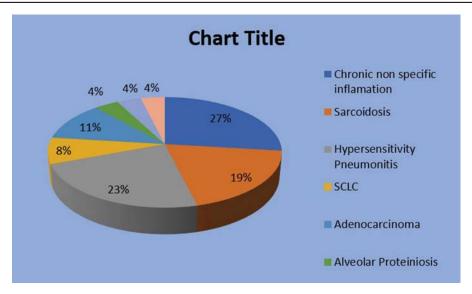
Results

This study included 26 patients. The diagnostic yield of TBLB was 73.1%. The different histopathological diagnoses included (Fig. 1) hypersensitivity pneumonitis (23.1%), sarcoidosis (19.2%), adenocarcinoma (11.5%), small cell lung cancer (7.7%), alveolar proteinosis (3.8%), alveolar hemorrhage (3.8%), organizing pneumonia (3.8%), and chronic nonspecific inflammation (26.9%).

The median and age range of the studied patients was 42.50 (20–72 years) and the mean age±SD was 45.62 ±13.816 years. Regarding sex distribution, the study included 17 (65.4%) female patients and nine (34.6%) male patients. Also, this study included three (11.5%) ex-smokers, 17 (65.4%) patients who were nonsmokers, and six (23.1%) smokers. There was no significant statistical correlation between age, sex, smoking history, and different histopathological diagnoses.

Regarding the predominant CT finding of among the study patients, out of 26 patients, 15 (57.7%) patients were GGO, whereas 11 (42.3%) patients indicated an alveolar-filling pattern with significant ($P=0.008$) positive correlation between the CT predominant pattern and the different histopathological diagnoses (Table 1). On the other hand, there was no statistical significant correlation between the predominant distribution of CT pathology and histopathological diagnosis. The

Figure 1

Pie chart showing the different histopathological diagnoses obtained by TBLB among the study population. SCLC, small cell lung carcinoma; TBLB, transbronchial lung biopsy.

Table 1 Predominant computed tomography findings among histopathological subgroups of the study population

Predominant CT finding	Histopathological findings [N (%)]								Total
	NSIP	Sarcoidosis	HP	SCLC	Adenocarcinoma	AP	AH	OP	
Alveolar-filling opacity	3 (42.9)	0 (0.0)	0 (0.0)	2 (100)	3 (100)	1 (100)	1 (100)	1 (100)	11 (42.3)
Ground-glass opacity	4 (57.1)	5 (100)	6 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (57.7)
Total	7 (26.9)	5 (19.2)	6 (23.1)	2 (7.7)	3 (11.5)	1 (3.8)	1 (3.8)	1 (3.8)	26 (100)
P value	0.008 (statistically significant)								

AH, alveolar hemorrhage; AP, alveolar proteinosis; CT, computed tomography; HP, hypersensitivity pneumonitis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; SCLC, small cell lung carcinoma.

Table 2 Other associated computed tomography findings among histopathological subgroups of the study population

Other associated CT finding	Histopathological findings [N (%)]								Total (n=26)
	CNSI (n=7)	Sarcoidosis (n=5)	HP (n=6)	SCLC (n=2)	Adenocarcinoma (n=3)	AP (n=1)	AH (n=1)	OP (n=1)	
Bilateral upper lobe (UL) nodular infiltrate	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Bilateral UL reticulate ions	1 (14.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)
Focal areas of air trapping	1 (14.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)
Lymph node enlargement	5 (71.4)	5 (100)	0 (0.0)	1 (50.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (100.0)	14 (53.8)
Right UL cavitary lesion	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)

AH, alveolar hemorrhage; AP, alveolar proteinosis; CNSI, chronic non-specific inflammation; CT, computed tomography; HP, hypersensitivity pneumonitis; OP, organizing pneumonia; SCLC, small cell lung carcinoma.

other associated chest CT findings are shown in Table 2. Out of 26 studied patients, 14 (53.8%) patients had lymph node affection with a positive significant correlation between lymph node enlargement in CT and histopathological diagnosis (P=0.029).

Bronchoscopic findings included mucosal nodules in seven (26.9%) patients and the other remaining nodules in 19 (73.1%) patients. There was no significant statistical correlation between bronchoscopic mucosal affection and histopathologic diagnosis.

The complications from TBLB included the pneumothorax [four (15.4%) patients] and bleeding [two (7.7%) patients].

Discussion

The aim of the present study was to evaluate the diagnostic yield of fiberoptic bronchoscopy (FOB) in patients with GGO and/or alveolar-filling opacity for histopathological diagnosis and find out its complications.

Regarding predominant CT findings in the present study, 15 out of 26 (57.7%) patients were GGO, whereas 11 (42.3%) patients had alveolar filling. The present study showed that HRCT scans provide accurate diagnosis in a greater number of patients with statistically significant positive correlation between the predominant CT finding and final diagnosis (P=0.008). This was due to the fact that the HRCT scan can examine the lung parenchyma so minutely that the appearance of 'ground glass' is equated histologically with a cellular reaction, whereas a 'reticular nodular' appearance denotes more advanced or less cellular fibrotic areas. Moreover, CT scans can define areas of the lung most involved with inflammation, so that biopsies can be directed to these locations [15].
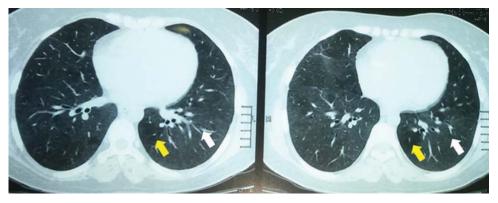
TBLB was done in all patients and the samples were sent for histopathology, and the diagnostic yield was 73.1%; the reason for failure in 27% of patients was due to the inadequate quantity of lung parenchyma for a meaningful histological analysis. Similarly, studies conducted by Joyner and Scheinhorn [16] and Ensminger and Prakash [17]) revealed that the diagnostic yield of bronchoscopic lung biopsy was 72 and 75%, respectively.

Regarding hypersensitivity pneumonitis cases in the present study, six out of 26 (23.1%) patients were diagnosed as hypersensitivity pneumonitis (Fig. 2) with a mean age of 42.83 years (±16.666 SD) and all patients were females; the predominant CT finding was GGO in all cases and the associated findings were bilateral upper lobe (UL) reticulations (16.7%) and the focal area of air trapping (16.7%). Similarly, in a study performed by Abd El-Kareem et al. [18], the age range was 15–60 years with a significant female predominance (90.7%). The most common HRCT pattern was GGO with mosaic parenchyma (41.86%), followed by GGO with centrilobular nodules (20.93%), then isolated diffuse GGO (11.62%), GGO with traction bronchiectasis (9.3%), GGO with consolidation (6.97%), GGO with reticulations (4.65%), and GGO with cysts (4.65%).
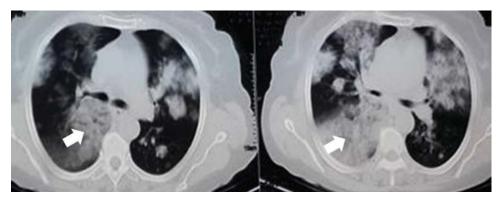
Although in a study performed by Lynch et al. [19], hypersensitivity pneumonitis was diagnosed in 11 out of 31 symptomatic pool employees by HRCT and TBLB. The abnormality consisted of fine, ill-defined centrilobular nodules. The extent of abnormality ranged from subtle nodularity to moderately profuse nodules.

Regarding sarcoidosis cases in this study, five (19.2%) patients were diagnosed with sarcoidosis with a mean age of 40.60 years (±8.081 SD), whereas 60% of the patients were females and 40% were males. GGO was the predominant CT finding associated with lymph node affection in all cases. Although in a study by Muller et al. [20] on 25 patients with biopsy-proved pulmonary sarcoidosis, the mean age was 45 years (±13 SD) and 12 patients were females and 13 were males. The CT scan showed lymph node enlargement in 20 patients. Regarding parenchymal affection, they concluded that the characteristic CT appearance of

Figure 2

Female patient, 36 years old, an ex-smoker, presented with dyspnea and cough for 1 year, no pulmonary hypertension, and no history of bird contact. The CT chest showed ground-glass opacification (white arrows) as the predominant pattern with focal areas of air trapping (yellow arrows). No abnormal bronchoscopic findings were investigated. The histopathological results of TBLB revealed hypersensitivity pneumonitis. CT, computed tomography; TBLB, transbronchial lung biopsy.

Figure 3

Female patient, 66 years old, nonsmoker, presented with dyspnea and was productive for 1 year with an excessive amount of frothy whitish expectoration associated with a history of loss of weight. The CT chest showed an alveolar-filling opacity (white arrows) as the predominant pattern. The histopathological results of TBLB revealed adenocarcinoma in situ, which was mostly serous. CT, computed tomography; TBLB, transbronchial lung biopsy.

pulmonary sarcoidosis consists of small nodules and irregular linear densities along the bronchovascular bundles.

In the present study, three (11.5%) patients were diagnosed with adenocarcinoma (Fig. 3) with a mean age of 69.00 years (±3.00 SD). A total of 66.7% of patients were males and 33.3% were females and their smoking prevalence was 33.3%. The predominant CT finding was alveolar filling in all cases associated with lymph node enlargement of 66.7%. In a study performed by Trigaux *et al.* [21], they investigated CT features of 42 cases with pathologically proven bronchioloalveolar carcinoma. The CT findings included a predominant solitary nodule or mass in 16 patients, lobar consolidation in 10 patients, multilobar consolidation in 13 patients, and a diffuse nodular pattern in three patients. Mediastinal enlarged lymph nodes were present in eight patients and two patients had pleural effusion.

In the present study, one (3.8%) female patient, 43 years old, was diagnosed with pulmonary alveolar proteinosis by bronchoalveolar lavage (BAL) and TBLB. Her chest CT revealed alveolar-filling opacity as the predominant pattern. The study performed by Holbert *et al.* [22] included 27 patients with pathologically proven pulmonary alveolar proteinosis. The predominant CT opacities included GGO in 100% of patients, air-space consolidation in 77.8% of patients, and fibrosis in 29.6% of patients. Mediastinal lymph node enlargement was visible in eight patients. They concluded that pulmonary alveolar proteinosis does not present with only alveolar disease. The CT appearance typically combines different types of opacities.

In this study, one (3.8%) female patient, 56 years old, was diagnosed with organizing pneumonia by BAL and TBLB. Her HRCT revealed alveolar-filling opacity as the predominant pattern. The study performed by Faria *et al.* [23] included 36 patients with biopsy-proven organizing pneumonia with a mean age of 56.2 years. The predominant CT finding was GGO (88.9%) followed by consolidation (83.3%).

Since its development nearly 40 years ago, flexible bronchoscopy became widely available commonly used by pulmonologists around the world. Flexible bronchoscopy is an extremely safe procedure as long as basic precautions are taken [24].

The present study reported that six (23.1%) patients developed complications with no mortality: two (7.7%) patients developed significant bleeding, whereas four (15.4%) patients developed the pneumothorax.

In the study performed by Hue [25], the most common complications were pneumothorax (11.8%), hemorrhage more than 50 ml (4.4%), premature ventricular contractions (2.9%), and mediastinal emphysema (1.5%).

Although in a study performed by Milmam *et al.* [26], complications related to TBLB were observed in 27 (6%) of the bronchoscopies. Twenty-six (5.8%) procedures were followed by the pneumothorax and there was 1 (0.2%) showing major bleeding with no observed mortality.

This study had some limitations, including first, the small sample size that may have an impact on the reliability of the results. Second, the small size of the

obtained specimens and the biopsy specimens is often subjected to punch and crush artifacts. To increase the diagnostic yield of TBLB and reduce the need to refer to surgical lung biopsy for diagnosis, advances in technology may be helpful, such as endobronchial ultrasonography, fluoroscopic, or CT guidance; future studies should be a greater implementation of the techniques of immunohistochemistry, molecular biology, and microarray to be applied even on tiny samples obtained from the TBLB and future studies are required to improve our knowledge about the benefits and indications of TBLB with a cryoprobe.

In conclusion, knowledge of the alveolar and/or GGO in the chest CT scan in addition to the presence of additional radiologic findings, together with a clinical history and histopathological examination of TBLB can often be useful in obtaining an appropriate diagnosis.

Acknowledgments

Conflicts of interest
There are no conflicts of interest.

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