RESEARCH ARTICLE

Transbronchial lung cryobiopsy guided by endobronchial ultrasound radial miniprobe in interstitial lung diseases: preliminary results of a prospective study

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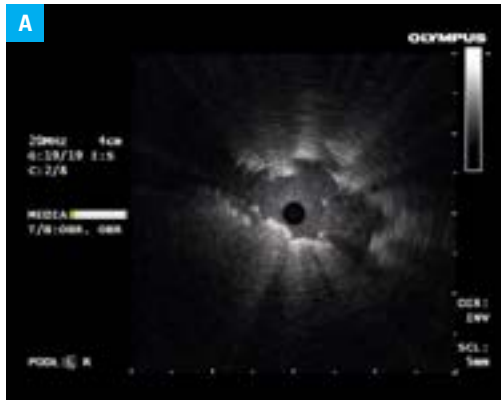
Introduction Interstitial lung diseases (ILD), also known as diffuse parenchymal lung diseases, are a heterogeneous group of diseases. Their common pathological mechanism is the presence of inflammation and/or fibrosis in the lung parenchyma. When clinical outcome and radiology findings (especially on high-resolution computed tomography [HRCT]) are not sufficient to establish proper diagnosis, a pathological assessment of the involved lung tissue may be necessary in selected patients. A transbronchial lung biopsy (TBLB) with endoscopic forceps is the most common approach. While its high value in diagnosing a few ILDs (such as sarcoidosis) is well established,[1,2] it is not recommended for diagnosing pulmonary fibrosis. According to American Thoracic Society / European Respiratory Society guidelines on the management of idiopathic pulmonary fibrosis, surgical lung biopsy (LB; usually video-assisted thoracic surgery LB [VATS-LB]) is recommended if HRCT results are inconclusive.[3] Another important indication for LB in patients with diffuse lung infiltrations is to exclude malignancy. Considering that the most common primary lung cancer, adenocarcinoma, is quite often diagnosed among patients with no smoking history and with radiological appearance of diffuse lung infiltrates mimicking ILD, a histological assessment is crucial in many cases.[4,5] Patients after VATS-LB require a few days of hospitalization and may develop complications, such as prolonged air leak and bronchopleural fistula, which in some cases necessitates reoperation and is associated with low but significant mortality risk.[6,7] Considering all these complications, it is necessary to develop minimally invasive methods of LB in ILD with pulmonary fibrosis.

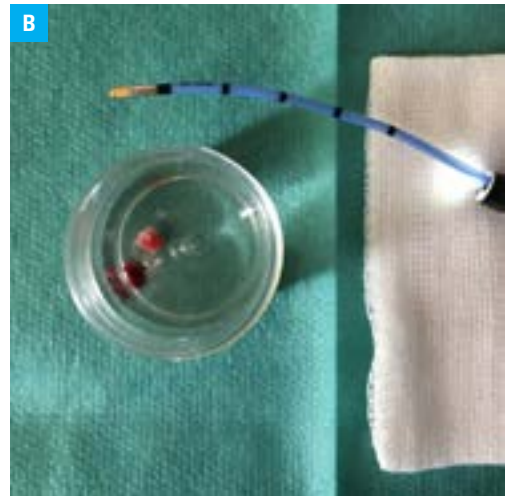
A biopsy with the use of a flexible cryoprobe was introduced to clinical practice a few years ago and initially proved its diagnostic value both in endobronchial and transbronchial tissue sampling.[8,9] Studies published to date have suggested that the diagnostic yield of transbronchial lung cryobiopsy (TBLC) in establishing proper diagnosis of ILD reaches 70% to 80%.[10]

A review of cryobiopsy literature revealed that there are no established standards for TBLC procedure. While the basic technique of TBLC is nearly the same, the approach differs as to prevention and management of the most common complications: pneumothorax and severe bleeding. The risk of pneumothorax increases when the cryoprobe is inserted too far into the bronchi and freezing hurts the visceral pleura. On the other hand, when the cryoprobe is too close to the pulmonary vessels, the risk of severe bleeding is higher.

There is no doubt that choosing a correct site for LB and controlling the cryoprobe's position during the procedure is crucial both for its efficacy and safety. The most common method of controlling the position of cryoprobe's tip is fluoroscopy.[11]

In our center, a radial endobronchial ultrasound miniature probe (r-EBUS) is routinely used for diagnosing peripheral solid and semi-solid lung lesions. A few years ago, we introduced





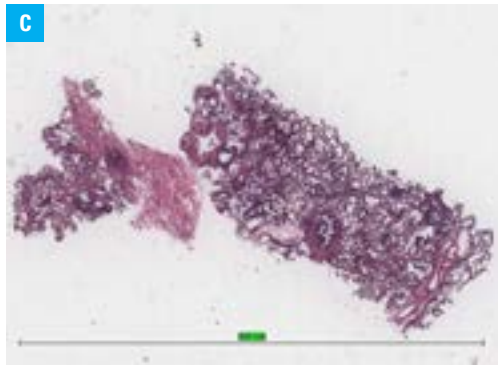


FIGURE 1 **A** – ultrasound imaging of interstitial lung infiltration obtained with radial endobronchial ultrasound miniprobe; organizing pneumonia was diagnosed. **B** – 2 lung tissue specimens obtained with the flexible cryoprobe inserted into the bronchofiberoscope; **C** – microscopic imaging of cryobiopsy (hematoxilin and eosin staining); organizing pneumonia was diagnosed. **A**, **B**, **C** – image courtesy of the Archives of the Pathology Department of Pulmonary Hospital, Zakopane

r-EBUS before performing conventional forceps TBLB for diagnosing patients with suspicion of ILD. In our experience, in some cases, if lung opacities are visible on ultrasound, r-EBUS allows the bronchoscopist to choose the best biopsy site. It is very useful in localizing vessels of the hilum and sometimes even shows the visceral pleura. Based on these observations, we designed a study for diagnosing ILDs with the use of TBLC without fluoroscopy but navigated by r-EBUS.

Patients and methods This study was designed as an open-label observational prospective trial. It was a single-center study conducted in Pulmonary Hospital in Zakopane, Poland. The study protocol was approved by the local ethics committee.

Consecutive patients with pulmonary infiltrates found on HRCT scans and suspected of ILD were enrolled if LB seemed to be necessary to establish a proper diagnosis. Patients were referred for LB on the basis of a clinical outcome and radiology assessed by experts in pulmonology and radiology according to the British Thoracic Society guidelines. The main exclusion criteria were: lack of the patient's consent, age below 18 years, and standard contraindications to invasive endoscopy such as abnormal hemostasis parameters, unstable cardiovascular disease, and/or heart failure. After the informed consent was obtained, the TBLC procedure was performed in the supine position under conscious sedation with intravenous fentanyl (0.05–0.1 mg) and midazolam (2.5–7.5 mg). Monitoring with pulse oximetry was mandatory with oxygen supply when necessary. The whole procedure was performed by a trained endoscopist with the assistance of 2 nurses. A flexible video bronchoscope (BFT180 or BFT190 Olympus, Tokyo, Japan) with a working channel of 2.8 to 3.0 mm was introduced by mouth, without endotracheal intubation. After topical administration of lignocaine (2%) and bronchial tree inspection, the ultrasound radial miniature probe UM-S20-20R (Olympus, Tokyo, Japan) was used. The probe was introduced to the selected lung region according to HRCT to choose the optimal site for LB (optimally if the lung infiltrates were visible on the ultrasound image and there were no vessels close to the lung opacities [FIGURE 1A]). Finally, the ultrasound probe was inserted as far as possible (sometimes a specific ultrasound sign of the visceral pleura was visible). A slow withdrawal of the ultrasound probe with control of the distance between pleura (if visible) and hilar vessels allowed us to identify the safest area for the biopsy. After the ultrasound examination, the flexible cryoprobe (diameter, 1.9 mm; length, 900 mm; ERBE, Tubingen, Germany) was introduced to the working channel of the bronchoscope. After placing its tip in the previously selected site (according to the r-EBUS examination), LB was performed with a freezing time of 5 to 8 seconds. We obtained 2 to 5 biopsies from 2 different segments of the same lobe. In the case of diffused lung infiltrates, the lower lobes were selected for biopsy. The distance from the visceral pleura was approximately 1 to 2 cm. The bronchoscope with the inserted cryoprobe and lung tissue adhering to the tip of the probe was taken out of the airways, and the specimen was placed in saline (FIGURE 1B). After withdrawing

the cryoprobe, the same scope was inserted into the bronchial tree again 15 to 30 seconds later to assess, and if necessary, manage the bleeding. The balloon catheter for lobar occlusion after TBLC was not used. For safety reasons, the double-lumen endotracheal tube was prepared in case of major bleeding requiring intubation and separated lung ventilation. The bleeding after biopsy was classified as minor, moderate, and major (<10 ml, 10–50 ml, and >50 ml, respectively). The chest X-ray due to the pneumothorax control was done within 2 to 4 hours after LB or immediately at the physician's discretion. After the procedure, the specimens were transferred from saline to formaldehyde solution (10%) and then sent to the Department of Pathology, where they were assessed by 2 independent pathologists after standard hematoxylin and eosin staining (FIGURE 1C). The final diagnosis was established by a multidisciplinary team comprising experts in pulmonology, radiology, and lung pathology.

Statistical analysis A statistical analysis was conducted on the basis of descriptive statistics as the mean with SD. The initial results were used to calculate the diagnostic yield.

Results From March to September 2017, 20 patients (9 men [45%] and 11 women [55%]; mean [SD] age, 60 [11] years) were enrolled to the study. The lung tissue obtained by r-EBUS–TBLC was found sufficient for pathological evaluation in all cases. The diameter of the specimen was 5 to 10 mm (mean, 7 mm). Histopathology results were conclusive in 16 cases (80%). Extrinsic allergic alveolitis was diagnosed in 4 patients; usual interstitial pneumonia, in 3; cryptogenic organizing pneumonia, in 2; sarcoidosis, in 2; and histiocytosis, hemosiderosis, rheumatoid arthritis-related ILD, nonspecific interstitial pneumonia, and disseminated adenocarcinoma, in 1 patient each. After 4 nondiagnostic biopsies (nonspecific interstitial lung fibrosis), the final diagnosis of cryptogenic organizing pneumonia, sarcoidosis, idiopathic pulmonary fibrosis, and extrinsic allergic alveolitis had been established on the basis of clinical presentation, radiological results, and exclusion of malignancy. So far, there has been no need for VATS-LB to confirm the diagnosis in any case. Complications included pneumothorax requiring a chest tube drainage in 1 patient (5%), and a minor bleeding in a few patients. No severe or moderate bleeding was observed.

Discussion While specimens obtained by conventional TBLB are often considered inadequate for histological evaluation, because they are too small and damaged by the forceps, those obtained by TBLC are bigger and free of crushing artifacts. In some studies, the results of TBLC in ILD were even comparable to those of VATS-LB and the procedure was safer.[10] A diagnostic yield of TBLC in available reports varied from 51% to 98%, and a complication rate (including the most common pneumothorax), from 0% to 33%.[11] The preliminary results of our study show the diagnostic yield at the level of 80% and the complication rate of 5%. Although the usefulness of TBLC for collecting adequate samples seems to be undisputable, there are no standards for its optimal performance. TBLC is typically performed with fluoroscopic guidance, endotracheal tube, or rigid bronchoscope intubation and deep sedation or general anesthesia. For safety reasons, it is important to know if the freezing tip of the flexible cryoprobe is distant enough from the chest wall or hilar vessels. In 26 TBLC reports from the period of 2009 to 2017 analyzed by Lentz et al,[11] fluoroscopic guidance was not used only in 2 studies (in one of them only in 40% cases). To our best knowledge, our approach whereby fluoroscopic guidance is replaced with r-EBUS is novel, simplifies the whole procedure, and avoids X-ray exposure. While the fluoroscopy provides guidance mainly for safety reasons, we expect that assessment of the lung with r-EBUS before TBLC may also sometimes help choose the most proper biopsy site (because some types of infiltrations are visible on ultrasound), and to increase its diagnostic yield.

In conclusion, our preliminary results show that the combination of r-EBUS and TBLC is a novel, reasonable, and safe technique for diagnosing ILD. However, because our study sample was relatively small, the results should be confirmed in a larger population.

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