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Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy: a novel approach for mediastinal lymph node sampling

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Abstract

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is preferred for evaluating malignant lymph nodes and staging of lung cancer. Nevertheless, larger tissue samples are increasingly needed, particularly for molecular analysis. We describe the feasibility, technical details, and complications of EBUS-guided transbronchial cryo-node biopsy (TBCNB) in four patients with mediastinal adenopathy. The samples obtained by EBUS-TBCNB in all cases were adequate for histopathological examination (HPE) and immunohistochemistry (IHC) staining. In case 1, HPE showed non-caseating epithelioid granuloma with giant cells and fibrosis consistent with sarcoidosis. Case 2 was diagnosed with adenocarcinoma with positivity for ROS1(D4D6). Case 3 showed features of metastatic adenocarcinoma from the breast (positive for Her2, ER, and GATA3). Case 4 was diagnosed with tuberculosis (necrotizing granuloma in histopathology, stain with Ziehl–Neelsen that showed few rod-shaped bacilli). Only one patient had minimal bleeding at the puncture site controlled with cold saline. There were no adverse events such as major bleeding, pneumomediastinum, or pneumothorax.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an established minimally invasive technique for mediastinal lymph node sampling. The pulmonology landscape has changed after introducing EBUS-TBNA for the diagnosis of mediastinal lymphadenopathy [1]. In certain conditions such as lymphoma and sarcoidosis, the diagnostic yield of EBUS-TBNA is low compared to the diagnostic yield for malignancy or other benign conditions [2]. Studies have shown that tissue sample is essential for making definite diagnosis as ultrasound features are overlapping in both benign and malignant lymph nodes [3,4]. There is also an increased demand for additional or larger samples in some instances due to the increasing need for molecular analysis [5]. Newer needles are under evaluation for a more extensive tissue acquisition with modifications in needle size, design, and tip [6].

We propose a novel approach for performing mediastinal lymph node sampling—endobronchial ultrasound-guided transbronchial cryo-node biopsy (EBUS-TBCNB) with 1.1 mm cryo-probe. This article describes the feasibility, technique, and complications of using EBUS-TBCNB in four patients with mediastinal adenopathy.

Case Series

Materials and Methods

Steps of EBUS-TBCNB

All the four patients underwent EBUS-TBNA (BF-UC180F; Olympus Medical Systems, Japan) initially under general anaesthesia, with laryngeal mask airway after obtaining informed written consent. The lymph node stations and characteristics are described in Table 1. Rapid onsite evaluation (ROSE) was done on the EBUS-TBNA sample, and also cell blocks were prepared from the material obtained.

For EBUS-TBCNB, we used a 1.1-mm flexible cryo-probe (Erbecryo 20402-401, Tubingen, Germany). After initial puncture with the EBUS-TBNA needle (Fig. 1A), a 1.1-mm cryo-probe was introduced into the working channel of the EBUS bronchoscope. The probe was advanced slowly towards the puncture site and pushed gently through the previous puncture site created by the EBUS-TBNA needle (Fig. 1B–D). Under real-time ultrasound guidance by the EBUS bronchoscope, the cryo-probe position was confirmed within the lymph node (Fig. 1E). The cryo-probe was activated for 3 sec, and the scope unit with the probe inside was pulled out (Fig. 1F). The specimens were thawed in saline and fixed in formalin. After obtaining the tissue, the puncture site was examined to see if any bleeding was present (Fig. 1G).

Specimen adequacy

The cytological samples obtained by EBUS-TBNA were adequate in all four cases. The ROSE of the cytological samples obtained from case 2 was diagnostic of adenocarcinoma.

Results

The samples obtained by cryo-nodal biopsy in all the cases were adequate for histopathological examination (HPE) and immunohistochemistry (IHC) staining. In our first case, HPE of the biopsy showed non-caseating epithelioid granuloma with giant cells and fibrosis (Fig. 2B); CD4 cells were more evident than CD8 cells (Fig. 2C) while few B lymphocytes highlighted with CD20 (Fig. 2D, E).

Table 1. Characteristics of lymph node, ROSE, and TBNCB in the four patients.

	Case 1	Case 2	Case 3	Case 4
Enlarged lymph node stations	7, 4L, 4R, 10R, 10L, 11L	7, 4L, 11L	4L, 11L	7, 4R
Size (cm)	>1	>1	>1	>1
Shape	Oval	Oval	Oval	Round
Margin	Indistinct	Distinct	Distinct	Indistinct
Echogenicity	Homogenous	Heterogenous	Homogenous	Heterogenous
Central hilar structure	No	Yes	No	No
Vascular pattern	Avascular	Avascular	Hilar	Non-hilar, central
Elastography pattern	II	III	III	II
Visual appearance of aspirate	Lymphoid	Lymphoid and bloody	Black	Lymphoid
Lymph node station from which EBUS-TBNA was done	7, 11L	7, 11L	4L, 11L	7
EBUS-TBNA needle size (G)	21	21	19	22
ROSE adequacy	Adequate	Adequate	Adequate	Adequate
ROSE diagnosis	Granulomatous inflammation	Adenocarcinoma	Atypical cells	Granulomatous inflammation with caseous necrosis
Lymph node station from which TBCNB was done	7	7	11L	7
Number of cryo-biopsies obtained	1	2	2	2
HPE diagnosis from TBCNB	Sarcoidosis	Adenocarcinoma	Metastatic adenocarcinoma	Tuberculosis
Complications	Nil	Nil	Nil	Minimal bleeding

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; HPE, histopathological examination; ROSE, rapid onsite evaluation; TBCNB; transbronchial cryo-node biopsy.

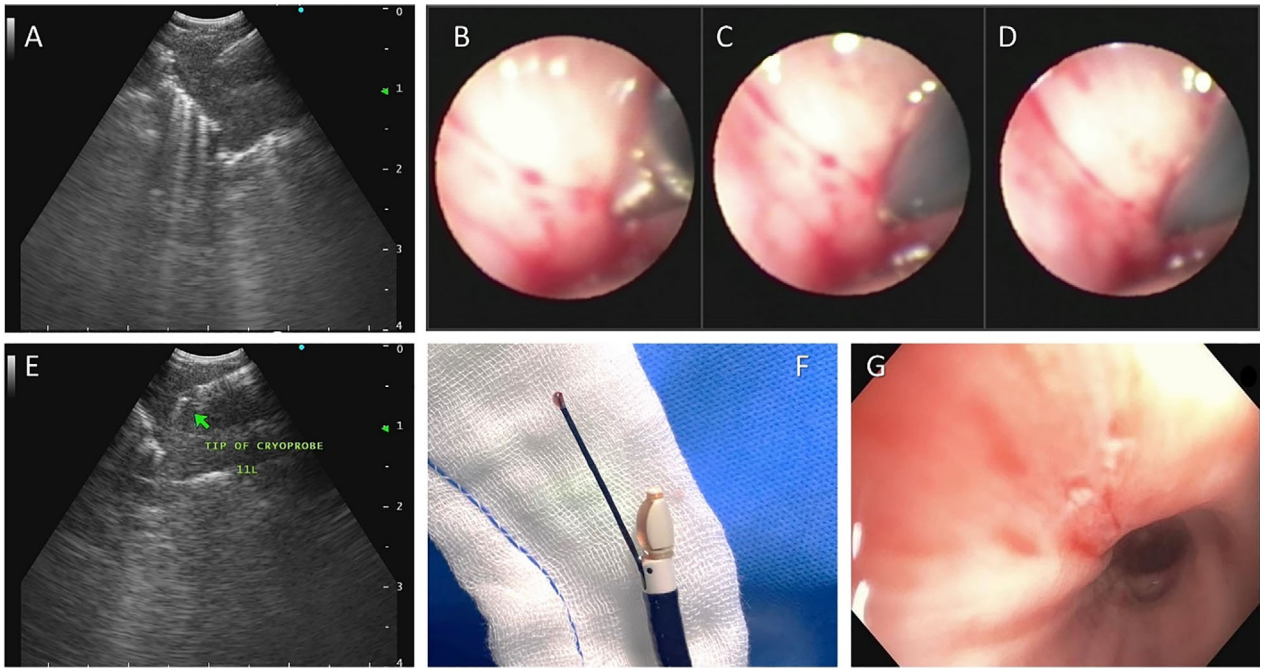

Figure 1. (A) Performing endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—EBUS image showing a 19-G needle in station 11L node; steps of inserting 1.1 mm cryo-probe through the puncture site made by TBNA needle, (B) tip of cryo-probe at the puncture site, (C) pushing the probe, and (D) a tip of cryo-probe completely inside the node. (E) EBUS image showing the tip of 1.1 mm cryo-probe within the lymph node. (F) Olympus EBUS scope (BF-UC 180F) with 1.1 mm cryo-probe in the working channel. The tip of the probe has the lymph node tissue obtained by cryo-nodal biopsy. (G) Bronchoscopic view of the puncture site after taking cryo-nodal biopsy.

A diagnosis of sarcoidosis was made based on the available data. The second case was diagnosed with adenocarcinoma with positivity for ROS1(D4D6) (Fig. 2G, H). The nodal biopsy obtained from the third case showed features of metastatic adenocarcinoma from the breast; tumour cells were positive for Her2, ER, and GATA3 (Fig. 2J–M). The fourth case was diagnosed with tuberculosis with necrotizing granuloma in the histopathology (Fig. 2O). CD8 cells were more evident than CD4 cells on IHC (Fig. 2Q, R). We were also able to stain with Ziehl–Neelsen that showed few rod-shaped bacilli (Fig. 2P).

Complications

Out of the four patients, only one had minimal bleeding at the puncture site controlled with cold saline. Apart from that, there were no adverse events such as major bleeding, pneumomediastinum, or pneumothorax. The post-procedure period was uneventful.

Discussion

EBUS-TBNA is now an established minimally invasive technique for the evaluation of mediastinal lymphadenopathy. Studies have shown that the overall diagnostic accuracy of EBUS-TBNA in the diagnosis of mediastinal and hilar lymph node pathology is around 80%. Disease-specific accuracy is 81.7%, 84%, and 78.9% in cancer diagnosis, non-small cell lung cancer (NSCLC), and non-cancer lesions [7]. In conditions such as lymphoma and fibrotic sarcoidosis, inadequate tissue samples may warrant repeated procedures or more invasive approaches such as mediastinoscopy and video-assisted thoracic surgery (VATS).

Alternative approaches have been attempted by many authors and have shown a better diagnostic yield. Studies have shown that in cases where EBUS-TBNA had a negative onsite evaluation, mini-forceps biopsy has successfully provided a diagnosis with no added adverse events. The first of these studies by Masahide et al. in which 22 patients underwent intranodal forceps biopsy (IFB) using a 19-gauge needle and 1.15-mm mini-forceps, this was without ultrasound guidance, and IFB obtained a diagnostic tissue in three patients in whom TBNA was negative [8]. Later, Herth et al. applied this technique via EBUS guidance using 19-gauge needles to create a tract for mini-forceps and the yield was 88% [9]. Subsequently, many studies have demonstrated a yield of 91–97% via IFB without any increase in time or any significant adverse events [10–12].

Zhang et al. have reported a case of EBUS-guided transbronchial mediastinal cryo-biopsy where the advantages of cryo-biopsy and EBUS were combined [13]. In this report, the

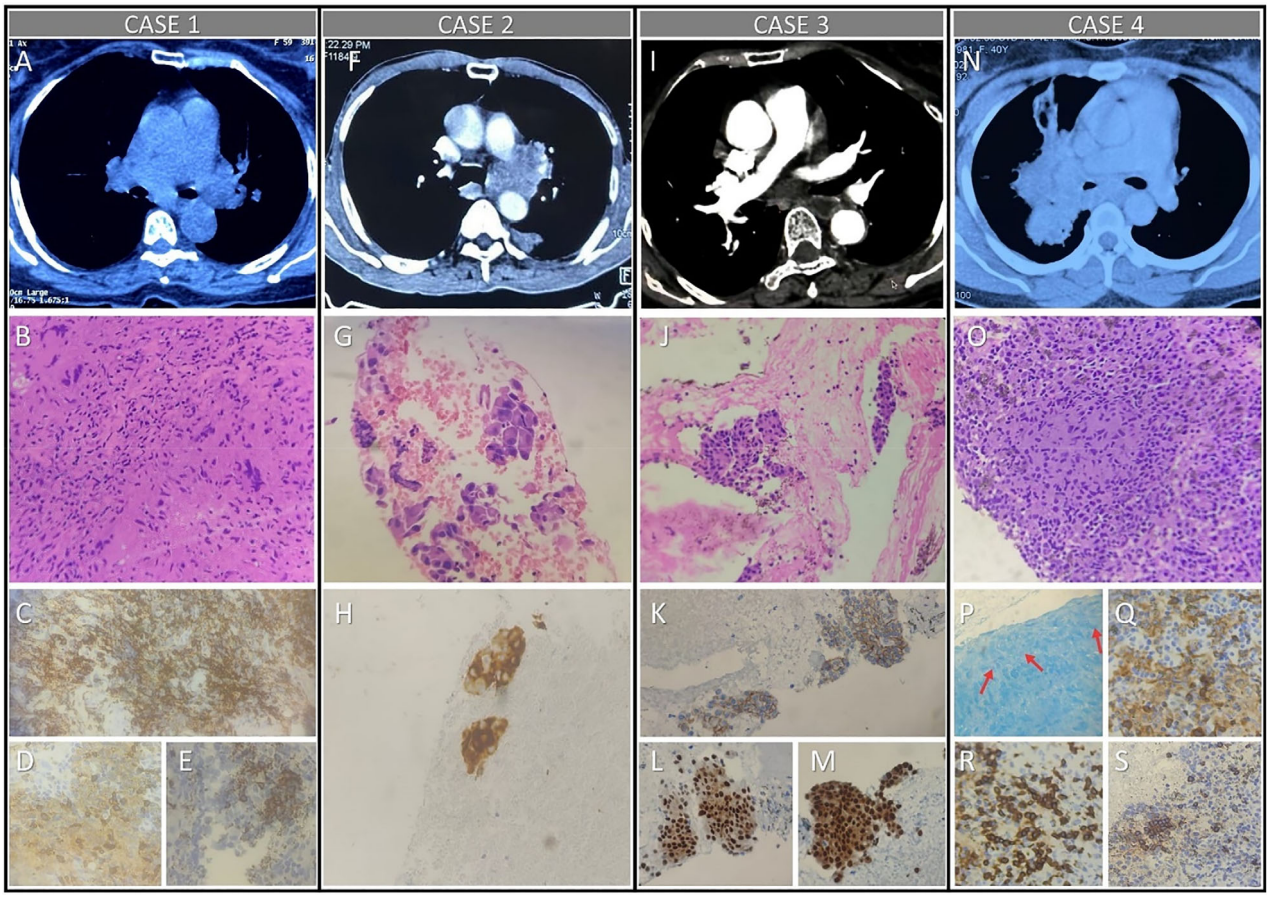

Figure 2. Case 1: (A) Non-contrast computed tomography (CT) thorax demonstrating sub-carinal and hilar nodes, (B) non-caseating epithelioid granuloma with giant cells and fibrosis (haematoxylin and eosin (H&E), 40×). CD4 cells (C) are more evident than CD8 cells (D) while few B lymphocytes are highlighted with CD20 (E). Case 2: (F) Contrast CT thorax showing left hilar mass with paratracheal lymph nodes, (G) adenocarcinoma cells (H&E, 10×), (H) with positivity for ROS1(D4D6) (10×). Case 3: (I) Contrast CT showing left interlobar node, (J) metastatic carcinoma from the breast (H&E, 10×), tumour cells are positive for Her2 (K), ER (L), and GATA3 (M). Case 4: (N) Non-contrast CT of the right para-hilar lesion with sub-carinal lymph node, (O) necrotizing granuloma (H&E, 40×), (P) Ziehl–Neelsen stain highlights few pink rod-shaped bacilli (red arrow), CD8 cells (Q) are more evident than CD4 cells (R) while few B lymphocytes are highlighted with CD20 (S).

author has performed transbronchial cryo-biopsy in a similar technique as ours, except using a high-frequency cautery needle knife to create an entry site for the cryo-probe.

To the best of our knowledge, this is the first case series where a 1.1-mm cryo-probe was utilized for transbronchial cryo-biopsy via EBUS. The procedure is not technically challenging, as it involves the same steps as that of EBUS-TBNA, except that a 1.1-mm cryo-probe is used instead of an EBUS-TBNA needle. The orifice created with the 21-gauge needle during the initial EBUS-TBNA needle puncture was adequate to pass the cryo-probe. The scope's deflexion angle did not get altered with the flexible cryo-probe in the working channel, which helped us maintain a proper view of the lymph node.

The samples obtained by nodal cryo-biopsy in all our patients were adequate to run IHC. With the challenge of sub-optimal tissue samples in some instances with EBUS-TBNA, nodal cryo-biopsy can provide adequate tissue for HPE.

In conclusion, our novel approach of obtaining tissue samples using EBUS-TBNCB helps retrieve larger biopsy specimens compared to EBUS-TBNA. The procedure is technically feasible and can be safely performed by the user having a good competency in performing EBUS. However, more extensive controlled trials are required to evaluate this technique's diagnostic accuracy compared to conventional EBUS-TBNA before recommending it for routine clinical practice.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this manuscript and accompanying images.

Author Contribution Statement

Hari Kishan Gonuguntla and Milap Shah conceptualized the work. Hari Kishan Gonuguntla, Milap Shah, Nitesh Gupta, and Sumita Agrawal acquired and analysed the data and revised it critically. Venerino Poletti and Gustavo Cumbo Nacheli guided the concept of work and revised it critically. The final version is approved by all the authors.

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