Primary Mediastinal Large B-Cell Lymphoma Achieved by Non-Cautery Assisted Transbronchial Mediastinal Cryobiopsy

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Established Facts

- Transbronchial mediastinal cryobiopsy has improved diagnostic yield compared to needle aspiration, particularly in uncommon tumors and benign disorders.
- Cautery-induced airway incision is required for this technique, which is normally time-consuming and increases operative difficulty.

Novel Insights

- New information: Transbronchial mediastinal cryobiopsy without cautery-induced airway incision might be a novel approach for mediastinal sampling.

Keywords

Endoscopic ultrasound · Cryobiopsy · Mediastinal lesion

Abstract

Transbronchial mediastinal cryobiopsy is a novel sampling strategy that shows improved diagnostic utility for mediastinal lesions, particularly in rare tumors and benign disorders, as compared to standard endobronchial ultrasound-guided transbronchial needle aspiration. During this procedure, electrocautery incision is frequently needed to advance the cryoprobe through the airway into the mediastinal lesion, which however results in increased operative difficulty and prolonged procedural time. Here we present a case of mediastinal large B-cell lymphoma successfully diagnosed by transbronchial mediastinal cryobiopsy without cautery-induced airway incision.

Introduction

Minimally invasive endoscopic biopsy, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), is currently recommended as the best first mediastinal sampling approach for lung cancer...
staging [1, 2]. Despite of the excellent accuracy in malignancy, its diagnostic yield for mediastinal diseases with other etiologies might be restricted due to the relatively limited materials retrieved by needle aspiration [3]. Aiming at larger, intact mediastinal materials, we have developed a novel mediastinal sampling strategy: EBUS-guided transbronchial mediastinal cryobiopsy [4, 5]. This technique has been proven to be safe and capable of offering a better diagnostic yield compared to standard needle aspiration biopsy [6]. During this procedure, cautery-induced airway incision is necessary for inserting the biopsy cryoprobe into the mediastinal lesion, which is associated with higher technical demands and longer operating time. Here we present a case of successful cryo-sampling of mediastinal lymphadenopathy without cautery-induced airway incision.

**Case Report**

The patient was a 64-year-old female who had no smoking history and was admitted to our hospital because of cough and dyspnea. She denied other complaints and was not on any medications. Laboratory examinations showed hemoglobin 87 g/L, NSE 73.6 ng/mL, LDH 947.2 IU/L, and IgE 640 IU/mL, with no other abnormal findings. A chest contrast-enhanced CT revealed mediastinal and bilateral hilar lymphadenopathies with slight and heterogeneous enhancement during the arterial phase, bilateral pleural effusion, and left inferior pulmonary inflammation (Fig. 1a). A contrast-enhanced CT of the abdomen and pelvis discovered retroperitoneal, mesenteric, pelvic, and bilateral inguinal lymphadenopathies.

No preprocedure antibiotic drug was used. The regular bronchoscopy resulted in no positive finding. Therefore, an EBUS bronchoscopy was conducted under conscious sedation with intravenous midazolam, and the subcarinal lesion (Station 7) was localized. After four passes of TBNA with a 21-gauge needle (Biostar-S217, Broncus, China) (Fig. 1b), we advanced its sheath along with the needle stylet into the lesion, which was visualized with the EBUS scope. Thereafter, we pulled out the stylet of the TBNA needle, leaving the sheath...
in the target lesion that served as a working cannula for cryobiopsy (Fig. 1c). The cryoprobe was then advanced into the target lesion via the needle sheath under the real-time supervision (Fig. 1c). After cooling down to −60°C for 7 s, the cryoprobe tip attached with the rapidly frozen material was extracted from the biopsy site (Fig. 1d). The specimen was obtained by thawing in saline and being fixed in formalin. The time needed for needle aspiration was 9 min, while it took only 1.3 min for cryobiopsy. The whole procedure was well-tolerated, and the only adverse event was minor bleeding that stopped spontaneously without pharmacological intervention. In addition, no major complications were observed right after the procedure and during 1-month follow-up.

Histological examination of TBNA samples showed squeezed and deformed atypical cells (Fig. 2a). The specimens from cryobiopsy suggested a diagnosis of non-Hodgkin’s lymphoma (Fig. 2b). Immunohistochemistry staining indicated CD20(+), CD79α(+), CD3(+), CD43(+), BCL-2(+), BCL-6(+), CD10(−), MUM1(+), Cyclin D1(−), Ki-67(+), CK(−), and EBER(−), confirming diffuse large B-cell lymphoma (Fig. 2c). This patient was referred to the Department of Hematology for further investigation and treatment.

Discussion

Current non-small cell lung cancer guidelines recommend endoscopic needle aspiration biopsy as the initial test for mediastinal staging. However, the small volume of the samples retrieved by TBNA only allows for cytological evaluation, which might limit its diagnostic utility in non-lung cancer lesions [7]. Accordingly, the largest meta-analysis on the diagnostic utility of EBUS-TBNA for lymphoma reported a pooled sensitivity of 66.2% [8]. Notably, a recent study has shown significantly improved specimen quality and diagnostic yield of mediastinal forceps biopsy, particularly in lymphoma and sarcoidosis, which highlights the clinical value of the acquisition of sufficient tissue samples [9].

Previously, we have shown that transbronchial mediastinal cryobiopsy is capable of providing the largest mediastinal materials among the minimally invasive biopsies, which contain more histopathologic characteristics and allow for further molecular and immunological evaluations [6]. Consequently, this technique has a superior overall diagnostic yield compared to traditional needle aspiration approach, particularly in patients with rare tumors and benign disease. In accordance, a definitive diagnosis of mediastinal large B-cell lymphoma was only achieved by mediastinal cryobiopsy but not needle aspiration in our case.

In theory, increased needle passes and the application of rapid on-site evaluation would improve the diagnostic ability of EBUS-TBNA. However, our procedure followed the current guideline, which indicated that medi-

![Fig. 2. a] H&E staining of the specimen from EBUS-TBNA. b] H&E staining of the specimen from non-cautery assisted transbronchial mediastinal cryobiopsy. c] Immunohistochemistry staining of the specimen from non-cautery assisted transbronchial mediastinal cryobiopsy. Scale bars = 30 μm. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.
astinal sampling without rapid on-site evaluation would have no negative impact on the diagnostic ability of TBNA and a minimum of 3 separate needle passes are required in this situation [10].

Similar with mediastinal forceps biopsy, the major technical challenge of the mediastinal cryobiopsy procedure is how to penetrate the cryoprobe through the airway wall or lymph node capsule. Two case series have reported the application of mediastinal cryobiopsy without bronchial wall incision, which was done by advancing the cryoprobe through the puncture site created by the EBUS-TBNA needle [11, 12]. However, it should be noted that prior studies have reported a 28% failure rate of mediastinal forceps biopsy due to an inability of inserting the biopsy instrument into the adjacent lymph nodes via the TBNA puncture site in the bronchial wall [13, 14]. Therefore, it might also be hard to pass the cryoprobe through the puncture site in certain cases, in consideration of the flexibility of the cryoprobe. To address this issue, we previously made a small cut on the tracheobronchial wall adjacent to the lesion with a high-frequency needle-knife, which allowed for the contact of the cryoprobe with the target [4]. However, cautery-induced incision results in unavoidable damages to the airway, the lymph node, and the adjacent mass, which increases the risk of adverse events such as bleeding and might negatively affect the specimen quality. Furthermore, this technique usually requires skilled interventional pulmonologists, and procedural success might not be easy to achieve for clinicians not familiar with EBUS and electrocautery.

In the current procedure, the working channel for the cryobiopsy could be established by simply advancing the sheath of the TBNA needle into the lesion and then pulling out its style after the completion of TBNA. The mediastinal lesion was reached via the pass of the cryoprobe through the channel, which is smooth without significant resistance. Similar with our prior experience on the cautery-assisted process, there was no difficulty in obtaining cryobiopsy samples from the small puncture site in our case, and no severe complication was encountered. This streamlined procedure is easy to handle and avoids additional injury to the airway and the adjacent tissue. Theoretically, it allows for the cryobiopsy of any mediastinal lesions that could be reached by the TBNA needle. Importantly, it significantly shortened the procedural time when compared to cautery-assisted mediastinal cryobiopsy (average 11.7 min) [6]. In summary, non-cautery assisted transbronchial mediastinal cryobiopsy might be a new sampling strategy for mediastinal diseases. However, prospective trials are required to confirm the feasibility and safety of this procedure.

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Statement of Ethics

This case was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The data collection was approved by the Ethics Committees of the Third Military Medical University (2019-062-01), and written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jing Zhang, Zan-Sheng Huang, Xian-Li Wu, An-Mei Zhang, Wan-Lei Fu, and Gang Liu contributed equally to this work. Jing Zhang, Zan-Sheng Huang, Xian-Li Wu, An-Mei Zhang, and Ye Fan were involved in the study design. Zan-Sheng Huang and Ye Fan performed the procedure described. Jing Zhang, Xian-Li Wu, An-Mei Zhang, and Gang Liu collected data. Wan-Lei Fu and Ye Fan analyzed the data. Felix JF Herth provided helpful guidance and suggestions. Ye Fan wrote the first draft of the manuscript. Jing Zhang, Zan-Sheng Huang, Xian-Li Wu, An-Mei Zhang, Wan-Lei Fu, Gang Liu, Felix J.F. Herth, and Ye Fan edited and approved the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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