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Scientific letter

Positioning of EBUS-guided Cryobiopsy in the Diagnosis of Mediastinal Lesions: A First Approach

Posicionamiento de la criobioebus para el diagnóstico de lesiones y adenopatías mediastínicas, primera aproximación

Dear Editor,

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the principal technique used in the diagnosis of hilar and mediastinal lymph nodes and masses. However, the small sample sizes retrieved make EBUS-TBNA unsuitable for diagnosing some diseases, including lymphoma, rare tumors, granulomatous diseases,[1,2] and for re-staging lung tumors. Until now, the choice of technique for obtaining large samples has been EBUS intranodal forceps biopsy (EBUS-IFB)[3] or mediastinoscopy. However, a new technique, EBUS-guided transbronchial mediastinal cryobiopsy (EBUS-MCB) that can be used obtain a large sample with same rate of complications as EBUS-TBNA, has recently been introduced.[4] The first case report of EBUS-MCB was published in 2019 by Zhang and colleagues, who reported its use in primary mediastinal seminoma.[5]

To analyze the diagnostic yield of EBUS-MCB versus EBUS-TBNA in the diagnosis of lymphadenopathies and mediastinal lesions, we conducted a single-center, observational, prospective analytical study in the Hospital Universitario y Politécnico La Fe, Valencia, Spain. The study was approved by the Ethics Research Committee in October 2024. We included patients >18 years of age with at least one mediastinal lesion (≥1 cm in the short axis) and inadequate rapid on-site evaluation (ROSE) after ultrasound bronchoscopy. Patients with mediastinal cysts or abscesses and/or contraindications to endoscopy or mediastinal biopsy were excluded. We used Student's *t* test (statistical p-value <0.05) to analyze differences between cellularity, and designed an algorithm to position EBUS-MCB in the diagnosis of these lesions.

In all patients, an EBUS-MCB procedure was performed by an experienced bronchoscopist under conscious sedation using a convex probe ultrasound bronchoscope (BFUC180F; Olympus Medical systems, Japan). First, 3 passes of the nodes were made using a conventional EBUS-TBNA needle (19 G Vizishot 2 flex TBNA needle; NA-U403SX-4019). Our hospital performs about 100 EBUS-TBNAs per year. In all cases, ROSE of aspirated material was performed by an expert cytopathologist. Patients in whom ROSE did not yield a diagnosis or the sample was considered of inadequate quality (inadequate ROSE), cryobiopsy of the largest lymph node was performed, generally consisting of 3 cryobiopsies with a 1.1 mm cryoprobe and a freezing time of 7 s.

A total of 36 patients were enrolled. The mean age of participants was 54.6 years. Most of the lesions were lymphadenopathy located in mediastinal station 7 ($n = 13$), 4R ($n = 6$) and hilar lymphadenopathies 11L ($n = 4$). Other stations were 2R ($n = 1$), 4L ($n = 2$) and 3p ($n = 2$), 12R ($n = 1$), 11R ($n = 2$), and 10R ($n = 1$). In 4 patients, we biopsied 2 stations, 4R + 7 ($n = 1$) and 7 + 11L ($n = 3$). Most histopathological diagnoses were lung tumors (non-small cell lung cancer, predominantly adenocarcinoma, small cell lung cancer, and large cell neuroendocrine carcinoma) followed by granulomatous diseases. In 4 patients, the diagnosis was reached with EBUS-MCB only (lymphoma, arterial sarcoma, undifferentiated tumor, and small cell lung cancer). Samples were diagnostic in 80.5% of EBUS-TBNA procedures and 91.6% of EBUS-MCB procedures. Samples obtained by EBUS-MCB had higher cellularity than those obtained by EBUS-TBNA (p-value: 0.008). The most common adverse event observed was minor (5.5%) and medium bleeding (2.7%). No major complications were noted during the procedure. Only one (2.7%) patient presented persistent cough during the procedure.

EBUS-MCB is a new reality. Different sizes of needles have been used – 19G, 21G and 22G – and no differences have been observed among needle sizes. Freezing time is another controversy. The differences between centers range from 3 s to 10 s. Recently, Ariza-Prota et al.[7] published a study that aimed to standardize the EBUS-MCB procedure. Similarly to these authors, we use a 19G needle to create the pathway through which we introduce the 1.1 mm cryoprobe and freeze for 7 s.[6,7] Finally, the number of cryobiopsies varies among centers with a range of 1–5 cryobiopsies. To date, the number of samples recommended for obtaining the highest number of diagnoses with the lowest number of complications has not been described. In our hospital, we perform 2–3.[6]

EBUS-MCB has a good safety profile. Only mild complications, normally mild/moderate bleeding resolved during the procedure, have been described in the literature.[8,9] Yang et al.[8] reported that diagnosis was achieved in 47.7% of cases without severe complications, concluding that EBUS-MCB is safe and effective.

The quality of the sample obtained with EBUS-MCB is much better than that obtained with EBUS-TBNA, thus improving the number of positive diagnoses.[10] Specifically, we described statistical differences between cellularity in EBUS-MCB vs EBUS-TBNA. In our experience, we needed EBUS-MCB to diagnosis rare tumors, such as arterial sarcoma and undifferentiated tumor. Diagnosis of lymphoma has also been found to be greater with EBUS-MCB, allowing its characterization in >80% of cases.[7] In our case, the diagnosis of lymphoma was higher using EBUS-MCB (5.4% vs 2.7%), obviating the need for further diagnostic studies. For granulomatous diseases (sarcoidosis, tuberculosis, etc.), better results with EBUS-MCB have been reported in the literature,[7] although our results were the same for both EBUS-TBNA and EBUS-MCB.

Despite the support in the literature for the use of EBUS-MCB in obtaining histological samples, there are insufficient studies evaluating the cost-effectiveness of cryobiopsy in all EBUS cases. To its disadvantage, EBUS-MCB needs more equipment (a cryomachine,

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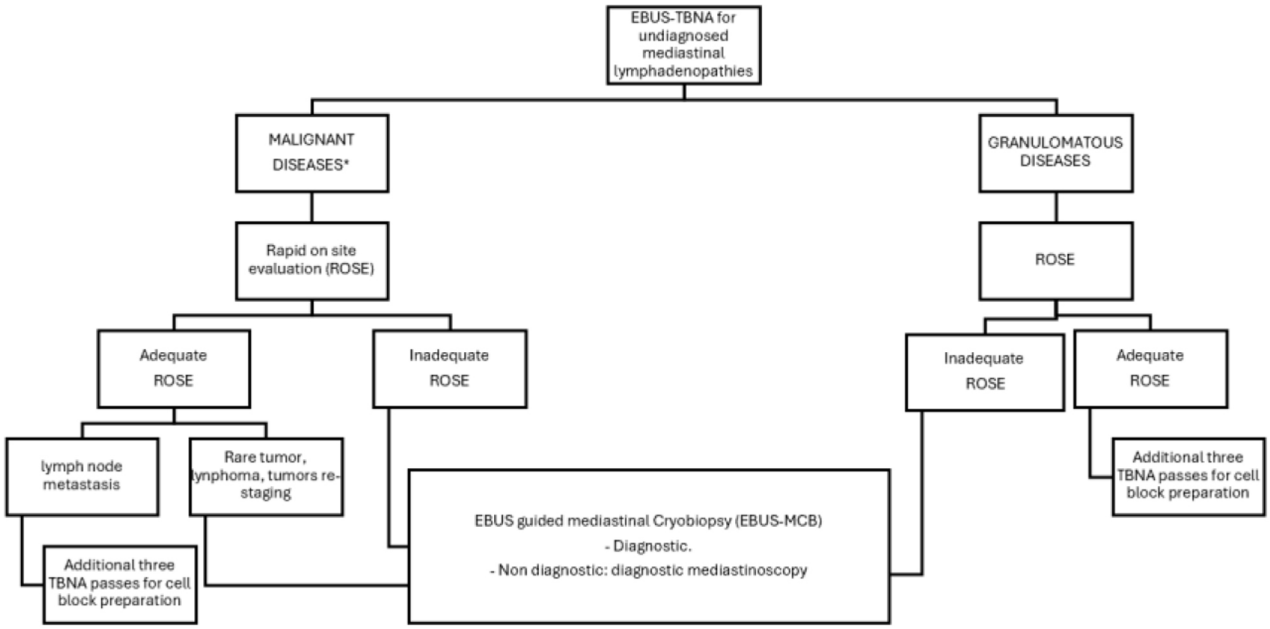

Fig. 1. Algorithm to perform EBUS-MCB for undiagnosed mediastinal lesions and lymphadenopathies. EBUS-MCB: endobronchial ultrasound-guided mediastinal cryobiopsy; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; ROSE: rapid on-site evaluation. *In case of clinical trial, perform EBUS-MCB.

cryogen, and 1.1-mm disposable cryoprobes), and the intervention lasts approximately 2 min more than EBUS-TBNA. The great advantage, though, is that it obtains larger samples. This is useful for reducing the diagnostic delay, especially in lymphoma where it avoids the need for further diagnostic studies,[11] for performing cancer molecular tests,[12] and for diagnosing rare disorders.[13] A recently published metanalysis found that EBUS-MCB improves tissue acquisition in mediastinal lesions (92% EBUS-MCB vs 81% EBUS-TBNA) and similar adverse event risks.[9]

As suggested in the literature, further studies are needed to evaluate uncertainties in the selection of suitable cases for EBUS-MCB, and optimal patient selection criteria remain to be defined.[12,14] For this reason, we propose an algorithm (Fig. 1) for the conduct of EBUS-MCB in patients with an inadequate ROSE, in clinical trials, and in the case of suspected lymphoma, rare tumors, or tumor re-staging.[5,15]

Our study has some limitations. This is a single-center study performed over a 1-year period in only 37 patients. The results of the study need to be replicated in other centers, and larger studies are needed before EBUS-MCB can be definitively included in the algorithm for the study of mediastinal lesions.

To conclude, EBUS-MCB is a novel technique for performing biopsies of mediastinal tumors and lymph nodes. It is useful for obtaining large samples with a higher percentage of cellularity than those retrieved with EBUS-TBNA, but with a similar rate of complications. This algorithm represents the initial phase in the establishment of standardized guidelines for the application of this novel technique.

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Authors' contributions

Selene Cuenca Peris contributed to the literature search, study design, data interpretation, and performed EBUS. Elsie Daviana Meneses Petersen contributed to data recollection.

Raquel Martínez Tomás, Andrés Briones Gómez and Enrique Cases Viedma performed EBUS.

Monica Bauza and Mireya Prieto Rodríguez analyzed all samples, and P. Alessandra Benini Padilla collected all pathology data.

Conflicts of interest

The results presented have not been previously published. The authors declare no competing interests.

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Selene Cuenca Peris [a,*], Monica Bauza [b], Elsie Daviana Meneses Petersen [b], Paola Alessandra Benini Padilla [b], Raquel Martínez Tomás [a], Andrés Briones Gómez [a], Mireya Prieto Rodríguez [b], Enrique Cases Viedma [a]

[a] *Unidad de Endoscopias Respiratorias y Neumología Intervencionista, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[b] *Department of Pathological Anatomy, Hospital Universitario y Politécnico La Fe, Valencia, Spain*

* Corresponding author.
E-mail address: selenecp@gmail.com (S. Cuenca Peris).