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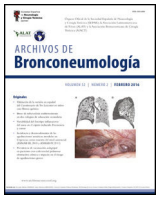

Scientific Letter

Ultrasonography-Guided Mediastinal Cryobiopsy in the Diagnosis of Mediastinal Diseases: Case Reports of 200 Cases

To the Director,

Endobronchial ultrasonography-guided mediastinal cryobiopsy or CRYO-EBUS is a rising technique, with an increasing number of publications on the subject since 2020 when the first case was reported by Zhang et al. reaching the diagnosis of a seminoma by using this technique.[1]

Currently, there are alternatives to this procedure, such as mediastinoscopy, which is still considered the gold standard for exploration and staging of the mediastinum. More recently, transesophageal mediastinal cryobiopsy, as reported in a study of 31 patients by Salcedo et al.,[2] has shown promising results. The CRYO-EBUS technique is a procedure performed following the conventional EBUS-TBNA (endobronchial ultrasound-guided fine needle aspiration) and can be considered a valuable complement to it.

From April 2022 to June 2024, a total of 200 patients with mediastinal lesions were referred to our Interventional Pulmonology unit for ultrasonography-guided mediastinal cryobiopsy via bronchial or esophageal access depending on patient characteristics. All procedures were performed by the same operators and every patient signed informed consent for bronchoscopy. ROSE (rapid on-site evaluation) was performed only in certain cases.

67% were male with a mean age of 62.2 ± 11.6 years. In 73.5% of cases sedation was administered by the bronchoscopist. The most commonly used combination was midazolam and fentanyl with average doses of 5.68 ± 2.36 mg and 120 ± 5.30 mcg respectively. Transbronchial access was used in 90.5% of cases, and transesophageal access (CRYO-EUS) in 19 cases. The most frequently biopsied adenopathy was subcarinal in 61.5% of cases, followed by hilar adenopathy in 19%, paratracheal adenopathy in 11.5%, mediastinal mass in 7% and 2 cases in the aortopulmonary window. Ultrasound characteristics were analyzed, 58% being multilobulated, 25% oval, and 17% rounded. 63% of them all were homogeneously echogenic.

On average, 2.24 ± 1.30 needle passes and 3 ± 1.24 cryobiopsies were performed to obtain samples. The mean size of the samples was 0.192 ± 0.058 cm for needle biopsies and 0.43 ± 0.179 cm for cryobiopsies. Table 1 shows the anatomopathological results, with an overall diagnostic yield of 83% for punctures (EBUS-TBNA) and 96.5% for biopsies taken with cryoprobe (CRYO-EBUS). There were no complications in 83.1%.

In detail, for neoplastic diseases, cryobiopsy provided 27 more positive results (104 vs. 77) compared to conventional EBUS-TBNA; in the case of hematological malignancies, it allows a greater number of diagnoses and better characterization of these diseases.

Table 1
Results and Diagnoses Puncture and Cryobiopsy.

Diagnosis	Puncture	Cryobiopsy
Neoplasm	77 patients 4 lymphomas 2 metastases (thyroid and intestinal)	104 patients 5 lymphomas 7 metastases
Negative	33 patients	34 patients
Inflammatory/infectious	4 reactive histiocytosis 14 sarcoidosis 2 TB	26 reactive histiocytosis 5 anthracosis 1 silicosis 19 sarcoidosis 4 infections (3 TB, 1 actinomyces)
Inconclusive	32 patients	3 patients
Inadequate	38 patients	4 patients

Meanwhile, in benign pathology, there was an increase in diagnoses with cryosonde, not only of reactive pathology but also of granulomatous diseases such as sarcoidosis or tuberculosis.

Nowadays, with the development of personalized and precision medicine, it is increasingly important to develop techniques that allow obtaining samples of higher quality and quantity to perform the different immunohistochemical techniques necessary in lung cancer. In the study by Velasco et al.,[3] it was observed that the larger size of cryobiopsies allows better evaluation by pathologists for immunohistochemistry, molecular biology, and genetic material recovery, including PD-L1 determination. In our series, the difference in size is more than double, a difference of 0.238 cm in favor of cryobiopsies.

In our cohort, we observed a considerable increase in neoplasm diagnoses compared to fine needle aspiration guided by ultrasound. Cryobiopsy was notably proven to be superior at classifying other types of tumors and lymphomas. The study by Poletti et al.[4] of 48 patients and the study by Zhang et al.[5] of 197 patients, showed that cryobiopsy better diagnosed uncommon neoplastic diseases (those other than bronchogenic carcinoma) and lymphoproliferative syndromes.

When analysing the benign pathology in our case series, we found that cryobiopsy led to more diagnoses, with 19 cases of sarcoidosis, 4 infections (3 of them TB), 26 reactive histiocytosis, 5 anthracosis, and 1 silicosis, compared to the needle biopsy where occupational diseases such as anthracosis or silicosis were not diagnosed, and the amount of diagnosis of other diseases was lower. In fact, a systematic review by Ramarmuty et al.[6] analyzing 7 studies determined that this procedure is better than conventional biopsy for this type of pathology.

In general, cryobiopsy shows a considerable improvement in terms of samples reported by anatomic pathology as insufficient for diagnosis, inadequate or inconclusive.

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A clinical trial by Fan et al.[7] of 297 patients has recently shown that cryobiopsy improves the diagnosis of both malignant and benign diseases. Cheng et al.[8] conducted a comparative study of cryobiopsy versus mini-forceps with a total of 155 patients, showing that the diagnostic yield of cryobiopsy remained superior, especially in benign pathology.

As comparative data with the conventional EBUS-TBNA technique a 2016 systematic review and meta-analysis found yields from 60 to 87% including the combination of EBUS and EUS.[9]

Regarding complications, a meta-analysis of 555 patients conducted by Botana et al.[10] and a study of 869 patients by Chandragiri et al.[11] found that the number of complications was minimal and could be reduced to mild bleeding, possibly related to the needle passes. In our series, 16.9% presented some complication. Most of them were mild bleeding, which did not require extra maneuvers during the procedure, 3 pneumothoraces without the need for thoracic drainage, 1 pneumomediastinum and there was no death related to the technique.

Currently, the role of ROSE is controversial in the literature. In a study by Maturu et al.,[12] a potential algorithm to perform cryobiopsy based on ROSE results was presented. However, in a meta-analysis by Chandragiri et al.,[10] including 14 studies, only 2 routinely performed ROSE and one in selected patients.

In conclusion, mediastinal cryobiopsy is a cost-effective diagnostic procedure for mediastinal pathology, with a low complication rate, as demonstrated by this Spanish cohort. However, more studies are needed to establish firm criteria for designing algorithms that guide clinical decision-making in mediastinal pathology. In particular, we must delimit which cases would be susceptible to CRYO-EBUS after TBNA puncture. In this sense, we do not believe that all mediastinal exploration with EBUS is necessarily subsidiary to cryobiopsy sampling, because although, as has been demonstrated, the diagnostic yield would improve, the cost also rises considerably. Possibly the most reasonable and cost-effective indications will be those cases of mediastinal pathology suspicious of lymphoproliferative and benign neoplasia, as well as in cases of bronchogenic carcinoma in which extensive genetic and molecular biology studies are necessary.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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