Original Article

Mediastinal Sampling with Endobronchial Ultrasound in Cancer Patients: Is It Always Metastatic?

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Abstract

Objective. The overall management and prognosis of a cancer patient depends on the histopathology, molecular genetics and staging of the disease. Staging refers to the size and the spread of the cancer. Knowing the stage of the cancer helps us to determine the natural history of the disease and median survival. It also helps us plan the best treatment for the patient. Mediastinal staging with invasive modalities, like endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become important for appropriate tissue sampling in patients with mediastinal involvement in various benign and malignant diseases.

Methods. A retrospective, cross-sectional study was done in a single tertiary care cancer centre from January, 2018 to December, 2018.The patients were referred for mediastinal staging and/or for diagnostic evaluation. The procedure EBUS-TBNA with rapid on-site evaluation (ROSE) was done for 123 patients as a day-care procedure in the bronchoscopy suite of the institution.

Results. Out of the total of 123 cases that underwent EBUS, 119 patients had an EBUS-TBNA for lymph node assessment. Staging in lung cancer, breast cancer, colon cancer, renal cell carcinoma was done in 63 (52.9%) cases and diagnostic evaluation of either a mediastinal mass lesion or a lung mass with mediastinal extension of lymph nodal involvement was done in 56 (47.1%) cases. Out of the 63 cases those underwent EBUS-TBNA for staging, 39 (61.9%) cases were non metastatic; 15 (38.4%) were diagnosed with granulomatous inflammation and 24 (61.5%) cases had reactive lymphadenitis. The remaining 24 of 63 cases had metastatic disease. Out of the 56 cases for diagnostic evaluation, 17 (30.3%) had granulomatous inflammation, 7 (12.5%) had reactive lymphadenitis and 32 (57.1%) had malignant disease.

Conclusions. Tissue pathology is always the crux to label a patient with the appropriate diagnosis. Moreover, accurate tissue sampling is important for mediastinal nodes in a diagnosed malignant disease, like lung cancer and breast cancer. This will help in appropriate staging and choose the proper treatment strategy. **[Indian J Chest Dis Allied Sci 2020;62:193-196]**

Key words: Key words: Mediastinal staging, EBUS-TBNA, Non-metastatic, Cancer, Lung, Breast

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is performed to investigate mediastinal masses, to help diagnose mediastinal lymphadenopathy of unknown origin and in the staging of cancer to assess the potential for curative treatment. Conditions commonly associated with mediastinal lymphadenopathy include neoplastic disease of the lung or other organs, haematological conditions like lymphoma, infections, and granulomatous diseases, like sarcoidosis.[1]

Staging of the cancer is essential for the selection of the best available treatment options and for the prognosis. Mediastinal staging in oncology includes involvement of the ipsilateral and/or contralateral node including mediastinal, hilar and intra-pulmonary lymph nodes. Endobronchial ultrasound (EBUS) is an interventional pulmonology procedure used for the evaluation of the mediastinal lesions. It has been used since the last decade with an advantage of vision-directed invasive procedure. Since its inception, EBUS has been used extensively in multiple centres around the world with

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different procedure set up, heterogeneous patient population, disease status and by the clinicians with varied background knowledge and skill set. With the help of EBUS, both the mediastinal lymph nodes and mediastinal masses can be assessed for the diagnostic and staging purposes.

In our sub-continent, with a huge burden of infectious diseases including tuberculosis, it becomes even more critical to determine the aetiology of the mediastinal lesions; not only for the undiagnosed mediastinal lesions, but also in the background of malignant diseases, as these immunocompromised patients are equally susceptible to other atypical and atypical infections. In our country, there is paucity of data regarding the utility of this very important diagnostic procedure. Our case series is an attempt to highlight the importance of a definitive aetiology of the mediastinal lesions in various types of malignant and non-malignant lesions, and thus, to increase awareness amongst clinicians to pursue for a mediastinal tissue sampling using EBUS-TBNA.[1]

Material and Methods

A retrospective study was undertaken from January 1, 2018 to December 31, 2018 in a tertiary care referral hospital, specialised in oncology care from the eastern part of the sub-continent. The patients were either referred to the interventional pulmonology team for staging of a known malignant disease or under diagnostic evaluation interventional pulmonology team for mediastinal lesions. The procedure done was EBUS first followed by EBUS-TBNA.

Patients who had primary lung malignancy or any extra-pulmonary malignancy with radiological evidence of mediastinal lymph node involvement detected either on computed tomography (CT) scan or on positron emission tomography (PET) scan were included in the study. Patients with myocardial ischaemia, arrhythmias, cardiac failure, severe hypoxemia at rest, hamodynamic instability, coagulation disorders were excluded.

The procedure was postponed for at least six weeks after myocardial infarction (MI). For the patients on warfarin or anti-platelets like clopidogrel, the medication was stopped at least one week prior to the procedure. International normalised ratio <1.4 and platelet count of at least 50,000/mm^3 was acceptable for the procedure. Heparin needed to be stopped for six hours, low molecular weight heparin for 12 hours and antithrombin drugs and Xa inhibitors for two days prior to the procedure.

Performing the procedure of EBUS-TBNA is a team work involving Anaesthetist unit, the Interventional Pulmonology unit and the Cytology unit and done in the bronchoscopy suite in a day-care setting. Prior to the starting of the procedure, the anaesthesia team evaluated the patients and confirmed their fitness for the procedure. Thereafter, conscious sedation was given and the patient was monitored throughout the procedure.

Initially, white light flexible bronchoscopy was performed to clear the secretions from the trachea-bronchial tree and to rule out any endobronchial lesion. Bronchoalveolar lavage (BAL) was also done from the involved segments during this time. Thereafter, EBUS was started through the oral route. After introduction of the EBUS scope into the tracheo-bronchial tree, visualisation of all the lymph node stations was done, *i.e.* sub-carinal (station 7), right upper para-tracheal (station 2R), right lower para-tracheal (station 4R), left upper para-tracheal (station 2L), left lower para-tracheal or left aorto-pulmonary window (station 4L), bilateral hilar (station 10) and pulmonary region (station 11,12). Measurement of the involved lymph node or mass was done and then vision directed sampling was done through the working channel of the EBUS scope. TBNA procedure was performed by doing 3 to 5 needle jabs with the help of special EBUS-TBNA needle which has a length of approximately 4 mm (Figure). After the sampling from the involved region the specimen was sent for both slide assessment and cell block. Rapid onsite evaluation (ROSE) was done by the cytologist in order to determine whether sampling of the tissue has been adequate for the diagnosis. If not, additional TBNA jabs were done. The patient was kept under observation in the recovery unit for two hours after the procedure.

Every detail of the procedure including indications of the procedure, mediastinal stations that were sampled, number of samples taken, ROSE results and final cytology results, anaesthesia and the post procedure observations in the recovery documented were analysed in this retrospective study. The hospital information system for the EBUS-TBNA cases using inclusion and exclusion criteria as given above were included in the study cohort.

Results

Out of a total of 123 cases, 119 cases underwent EBUS-TBNA. Amongst the entire study cohort, 63 (52.9%) cases were done for staging purpose and 56 (47.1 %) cases were done for diagnostic evaluation. The positive yield of the EBUS-TBNA procedure was 100%. All these 119 cases had adequate sampling for the diagnosis. Four cases did not undergo TBNA because EBUS confirmed very small node <0.5cm in short axis diameter (SAD) with EBUS in real time analysis during the procedure and were excluded from this study analysis.

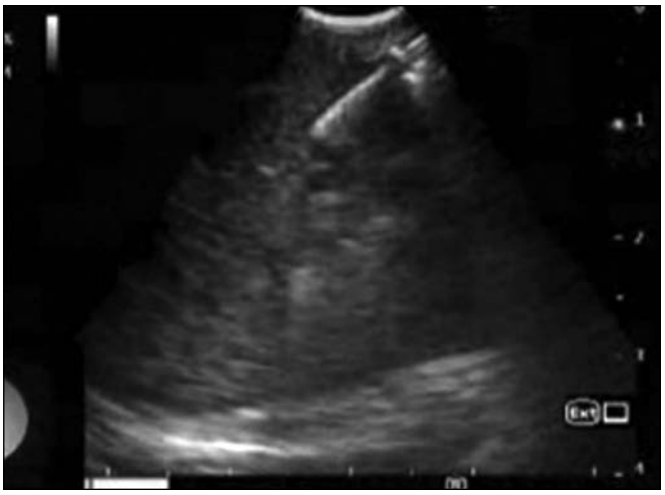

Figure. EBUS-TBNA done from the subcarinal lymph node: station 7.

Out of the 56 diagnostic cases, 17 (30.3%) had granulomatous inflammation, 7 (12.5%) had reactive lymphadenitis and 32 (57.1%) had malignant disease. Out of the 63 cases who underwent EBUS-TBNA for staging, 39 (61.9%) cases were non-metastatic, *i.e.* 15 (38.4%) cases were diagnosed with granulomatous inflammation, and the remaining 24 (61.6%) cases had reactive lymphadenitis. Out of the 15 patients with granulomatous inflammation, four cases had Mantoux negative status with bronchoalveolar lavage (BAL) negative for acid-fast bacilli (AFB) smear, GeneXpert®, AFB culture and fungal culture. These four cases were treated with systemic steroids for sarcoidosis and showed both clinical, radiological and spirometry improvement at the end of one year of treatment with gradual tapering of the steroid dose. The other 11 cases were treated for tuberculosis (TB) with anti-tubercular treatment (ATT) and showed complete resolution of both clinical symptoms and radiological features. Out of the 24 cases that had reactive lymphadenitis, nine cases had a positive microbiology on BAL culture. All the cases with reactive lymphadenitis were treated with appropriate antibiotics. The remaining 24 out of the 63 cases those underwent EBUS-TBNA for staging of cancer had metastatic disease.

One of the patient required a non-invasive bilevel positive airway pressure (BiPAP) support after the procedure for two hours. He received chemotherapy and radiation therapy after two days of the procedure. Post-procedure, all the patients were discharged from the bronchoscopy suite after four hours of observation in the recovery. None of the patients had to be shifted to the intensive care unit (ICU). There was no mortality or morbidity associated with this procedure.

Discussion

Different techniques exist for sampling of the mediastinum pathology. In view of many vital structures present in the mediastinum, invasive tissue sampling is a challenge. Invasive staging is frequently required to confirm or rule out the presence of the metastatic disease within the lymph nodes secondary to various forms of malignant diseases. Endobronchial ultrasound-guided transbronchial needle aspiration is a minimally invasive real-time technique for the cytodiagnosis of the mediastinal lesions and helps the clinician to get a definitive diagnosis.[1-3] Of the other modalities, the median sensitivity and specificity of CT for identifying involvement of mediastinal lymph node as part of the metastatic evaluation are 55% and 81%, respectively.[4] Imaging with PET-CT scan technique has observed a slightly higher specificity of 90%, but a lower sensitivity of 62%.[4] Unfortunately, this diagnostic accuracy is insufficient to guide the treatment decisions.

Endobronchial ultrasound-guided transbronchial aspiration with ROSE has emerged as a highly effective and safe technique for sampling peri-bronchial, mediastinal and lung masses for pathological examination. Recent studies[5-7] have revealed EBUS to be significantly cost-effective compared with prior gold standard techniques, like mediastinoscopy. Thus, EBUS-TBNA plays a pivotal role in the staging of not only lung cancer, but also other solid organ malignancies with mediastinal involvement, like breast cancer, renal cell carcinoma and colon carcinoma. Moreover, EBUS-TBNA has evolved as a very important diagnostic modality for the patients with treated cancer who develop mediastinal and hilar lymphadenopathy to avoid erroneous upstaging or misdiagnosis of cancer recurrence.[8]

In our case series, the diagnostic yield of the EBUS-TBNA has been as high as 100%. This has helped us in adequate staging and treatment of these cancer patients. Out of the total 63 cases for staging through EBUS, around 62% had a down staging of their malignant condition. Of the 39 down staged cases, 15 cases were that of granulomatous lymphadenitis and 24 cases of reactive lymphadenitis. This is a very important take-home message for our country as the infection rate of TB remains quite high when compared with the developed countries.

A review of the literature from India revealed that the most common aetiology of mediastinal lymphadenopathy was granulomatous disorder (53%), like tuberculosis and sarcoidosis; whilst malignancy was third in order of diagnosis (17%).[9-11] Out of the non-malignant mediastinal lesions in the general population, reactive lymphadenitis is the second most common aetiology following granulomatous disease.[10-12] In our study too, although being done in a tertiary care referral cancer centre, and thus,

having a selection bias in the study cohort, we found the commonest cause of non-metastatic mediastinal lesion to be reactive lymphadenitis followed by granulomatous inflammation. In the present study we found the non-metastatic lesions to be more prevalent than metastatic lesions (61.9% non-metastatic disease *versus* 38.1% metastatic disease on EBUS staging).

It needs to be emphasised that invasive sampling of mediastinal lymph node staging is the sheet anchor for the identification of either malignant or non-malignant disease. It will not only help in the prognosis and down the staging of the primary malignant conditions, but also help treating the alternative or additional benign diseases, like TB, sarcoidosis and reduce both psychological and pathological morbidity and mortality in these patients.

The limitation of the study includes retrospective cohort as well as selection bias as the data is from a single tertiary care cancer referral centre. In spite of this limitation, it was observed that benign mediastinal lesions are very common in the patients with a primary malignant disease.

The limitation of EBUS-TBNA as a procedure is quite similar to that of EUS-FNA (oesophageal ultrasound-guided fine needle aspiration) due to their inability to access some parts of the mediastinum. Compared with EUS-FNA, the posterior mediastinum along the oesophagus cannot be assessed with EBUS-TBNA. By combining EBUS-TBNA and EUS-FNA, the majority of the mediastinum is accessible.[13,14] However, even with the combination of EBUS-TBNA and EUS-FNA, the anterior mediastinum is not accessible.[13,14]

Another limitation of EBUS-TBNA is the size of the needle available for needle aspiration. In our current study population, we used the 22-gauge needle for all the cases. Although the histological cores can be obtained by the use of the internal stylet in most of the cases; sometimes the specimen might not be adequate for the diagnosis. Consequently, a repeat tissue sampling may be required which would mean longer duration of the procedure and longer anaesthesia time. The newer 19-gauge and 21-gauge needles may resolve these technical aspects by allowing the larger tissue sampling.[15]

Conclusions

Endobronchial ultrasound-guided transbronchial needle aspiration is a safe and minimally invasive procedure for sampling of mediastinal tissues. It should be considered for the evaluation of mediastinal lesions early in the diagnoses process along with other minimally invasive procedures. It spares more invasive procedures, like mediastinoscopy or video-assisted thoracic surgery for tissue sampling of the mediastinum.

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