Endobronchial ultrasound elastography in mediastinal lymphadenopathy: Report of two cases and systematic review of literature

Saurabh Mittal, Anant Mohan, Vijay Hadda, Karan Madan

Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Endobronchial ultrasound elastography is new ultrasound technology that is being reported recently for the evaluation of mediastinal lymphadenopathy during endobronchial ultrasound-guided (EBUS) transbronchial needle aspiration. This modality is based on the assessment of tissue stiffness that may be useful in differentiating benign from malignant lesions. Image generation leads to colored images with different colors signifying varying degrees of stiffness. The utility of this technique has been studied to differentiate between benign and malignant lymph nodes and various methods for representation of results which include visual color estimation, quantitative color estimation, and strain ratios have been described. Herein, we report two patients with mediastinal lymphadenopathy wherein EBUS elastography was employed. We also systemically review the studies describing this technique in differentiating benign from malignant lymph nodes.

KEY WORDS: Bronchoscopy, elastography, endobronchial ultrasound

Address for correspondence: Dr. Karan Madan, Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: drkaranmadan@gmail.com

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is routinely performed for evaluation of mediastinal lymphadenopathy of both benign and malignant etiologies.[1-3] Ultrasound guidance helps in improved localization of lymph nodes so that vascular puncture can be avoided and yield may be improved. Many patients have multistation lymph nodal involvement, and in this situation, sampling each node may not be practically feasible, and usually, the largest and most involved station is sampled based on the operator's discretion. Assessment of sonographic lymph node characteristics during EBUS TBNA has also been described that may help in differentiating various conditions.[4] EBUS elastography is a new modality which has been studied and proposed as a useful technique in differentiation of benign versus malignant mediastinal lymphadenopathy.[5-12] The proposed hypothesis is that neoplastic tissue has greater cellularity and vascularity which leads to increased stiffness. This stiffness measurement is the basic principle behind EBUS elastography. This technique leads to production of color images representing relative stiffness of tissue by structural deformation caused by compression or vibration. However, there is also concern that there may be limitations of this technique in this regard.[13] Herein, we report two patients with mediastinal lymphadenopathy wherein we performed EBUS elastography.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_349_17

How to cite this article: Mittal S, Mohan A, Hadda V, Madan K. Endobronchial ultrasound elastography in mediastinal lymphadenopathy: Report of two cases and systematic review of literature. Lung India 2019;36:149-53.

CASE REPORTS

Case 1

A 30-year old female presented with dry cough for 3 weeks. There was no history of shortness of breath and hemoptysis. She was a lifetime nonsmoker. She had been operated for breast carcinoma 2 years previously and had received chemotherapy. Tuberculin skin test was negative and serum angiotensin converting enzyme (ACE) level was 88 IU/mL. Computed tomography (CT) scan of the thorax demonstrated subcarinal and right paratracheal lymphadenopathy. EBUS elastography was performed at the time of lymph node localization (Olympus, Endoscopic Ultrasound Centre, EU-ME2 Premier Plus, Japan) for obtaining a qualitative pattern of color images.

During elastography, two vertical images are projected on the monitor. On the left side of screen, the B-mode image is seen [Figure 1, left panel] while on the right side, the color-coded image (elastography image) of stiffness is superimposed on the B-mode image [Figure 1, right panel]. On EBUS, a 13.6 mm × 16.0 mm subcarinal lymph node was identified which was heterogeneous in appearance with no coagulation necrosis sign or calcification. On elastography, the lymph node had a predominantly blue pattern with a strain ratio of 23 [Figure 1]. Cytopathological analysis of the EBUS aspirate demonstrated multiple nonnecrotizing epithelioid cell granulomas. A diagnosis of sarcoidosis was established.

Case 2

A 47-year-old female presented with a history of fever of 1-month duration associated with significant loss of weight and appetite. The patient was a lifetime never smoker and had no previous history of tuberculosis (TB). CT scan of the thorax demonstrated large lower right paratracheal lymphadenopathy. Induration on tuberculin skin test was 18 mm and serum ACE level was 28 IU/mL. EBUS examination showed a 22.0 mm × 35.0 mm lymph node at the lower right paratracheal lymph node station (4R) with central hypoechoic area without blood flow on color doppler suggestive of coagulation necrosis sign. On EBUS elastography, the lymph node had partly blue partly green pattern with a strain ratio of 13 [Figure 2]. Cytological analysis of the aspirate demonstrated multiple necrotizing epithelioid cell granulomas. A diagnosis of TB was made, and the patient was started on antitubercular therapy.

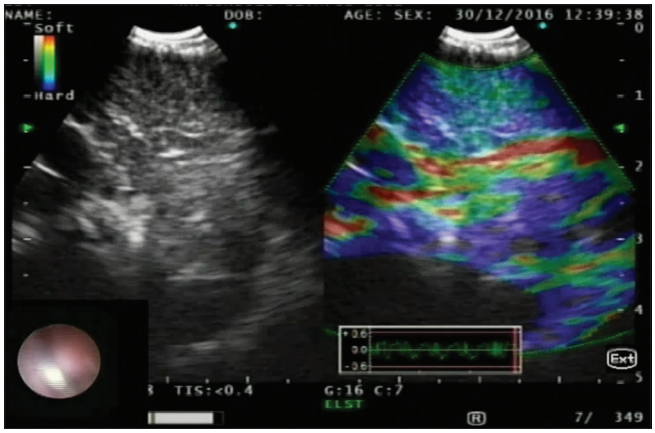

Figure 1: Endobronchial ultrasound-guided elastography view with screen split in two vertical portions. The left panel shows B-mode ultrasound while right panel shows colored representation showing predominantly blue pattern in Case 1

Systematic review

We performed a systematic search of the PubMed and EMBASE databases (2004–2017) to identify the studies reporting the utilization of EBUS elastography using the following search terms – ([“ebus” or “ebus-tbna” or “tbna” or “endobronchial ultrasound” or “endobronchial ultrasonography” or “endobronchial ultrasound guided” or “endoscopic ultrasound”] and [“elastography”]). The reference lists of the extracted studies and the author’s personal files were also reviewed. We excluded the following types of studies – (a) studies that did not report the utilization of EBUS elastography, (b) reviews or commentaries without any case description, and (c) language other than English.

After removal of duplicate citations, the citations were reviewed by their title and abstract, and whenever felt appropriate, the full texts were extracted and reviewed. Data were abstracted on a data extraction form and the following information were retrieved from the selected studies – (a) author, (b) year, (c) country, (d) number of patients, (e) number of lymph nodes, (f) method of elastography reporting, (g) whether strain ratio reported, (h) type of EBUS machine used, and (i) study conclusion.

The systematic review methodology is summarized in Figure 3. The details of the final selected studies for review are summarized in Table 1.

DISCUSSION

We describe two patients with granulomatous mediastinal lymphadenopathy and their EBUS elastography

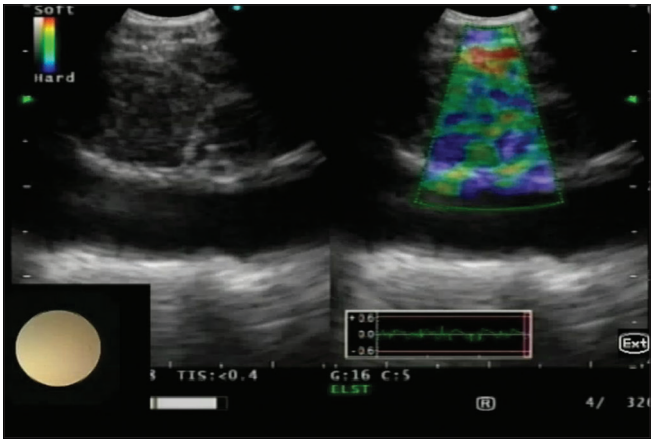

Figure 2: Endobronchial ultrasound-guided elastography view in Case 2 showing partly blue partly green pattern

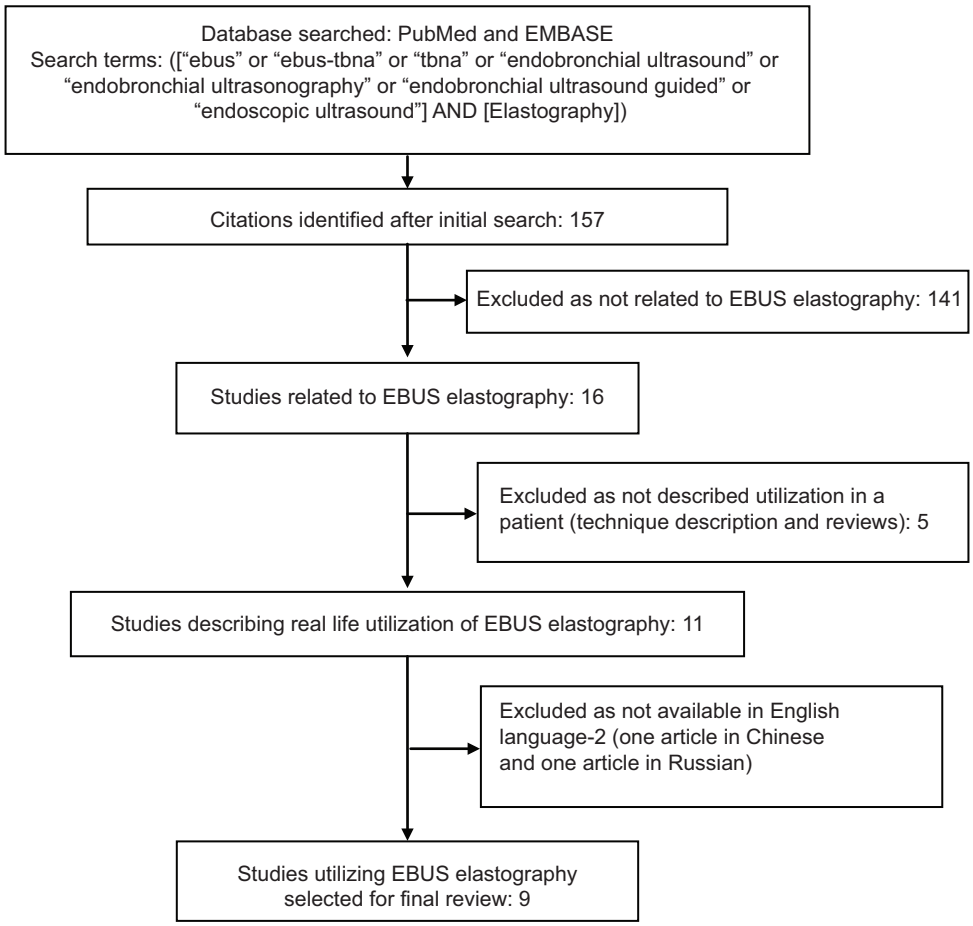

Figure 3: Methodology of systematic review of literature regarding endobronchial ultrasound elastography for mediastinal lymphadenopathy

characteristics. EBUS elastography is increasingly being investigated for its utility in evaluation of mediastinal lymphadenopathy. EBUS elastography is akin to clinical examination for peripheral lymph nodes where consistency of lymph nodes may suggest a likely etiology and hard lymph nodes are more likely to be malignant. Elastography measures strain (hardness) of the tissue and it has been shown in multiple studies that nodes appearing benign on elastography may harbor malignancy and vice versa.[5,6,8] The stiffness is represented by color-coded images and is displayed on the screen. The blue areas represent stiff tissue while intermediate and softer areas are represented in green and red, respectively. EBUS elastography works on the same principle in mediastinal lymph nodes which are not accessible for clinical examination. Endoscopic ultrasound elastography is a similar technique used by gastroenterologists and has been evaluated extensively.[15]

Various investigators have utilized different reporting methods for EBUS elastography findings. Based on predominant color on elastography, the nodes may be classified into three types: Type 1 predominantly nonblue, Type 2 partly blue partly nonblue, and Type 3 predominantly blue.[8] Type 1 nodes are mostly benign on pathological examination while majority of type 3 nodes may harbor malignancy. Another way of assessment is using the strain ratio which is calculated as hardness of lymph node compared to normal perinodal area.[6] The strain ratio is measured when good contact and appropriate compression of the transducer are achieved. The largest possible area within the lymph node is circled using the caliper, and similarly, a surrounding normal area is circled. The processor measures the strain of each area (A and B, respectively) and ratio is expressed as a value (B/A). This ratio is measured three times before nodal puncture and its mean value is reported. Quantitative color analysis is also a way of interpreting EBUS elastography. The lymph nodes are classified into four grades depending on dominant color pattern.[9] The proposed grading system is: 1 point when >80% of the area is green and yellow/red; 2 points when 50%–80% of the area is green and yellow/red; 3 points when 50%–80% of the area is blue; and 4 points when >80% of the area is blue. Higher grade of elastography features correlates with higher probability of malignancy. For the quantitative analysis, stiff area ratio (SAR) has also been described which is defined as stiff area (blue color pixel area) per lymph node area on the elastography.[7] The SAR is determined using an image software that provides percentage of various colors in an image. Another way of qualitative assessment is use of color score from 1 to 5 where 1 describes no blue while

Table 1: Systematic review of the studies reporting the utilization of endobronchial ultrasound elastography for mediastinal lymphadenopathy

Author and year	Country	Number of patients	Number of LNs	Method of elastography reporting	System used	Strain ratio reported	Remarks
Trosini-Désert *et al*., 2013[10]	France	10	13 Malignant 5 Benign 8	Color dispersion; 0-255 (0-blue, 255-red)	Pentax	No	Malignant node had elasticity ranging from 10 to 49 while benign nodes had 55-167
Izumo *et al*., 2014[8]	Japan	30	75 42 Malignant 33 Benign	Three types Type 1: Predominantly nonblue (green, yellow, and red) Type 2: Part blue, part nonblue (green, yellow, and red) Type 3: Predominantly blue	Olympus	No	In classifying Type 1 as "benign" and Type 3 as "malignant;" the sensitivity, specificity, PPV, NPV, and diagnostic accuracy rates were 100, 92.3, 94.6, 100, and 96.7%, respectively
Andreo García *et al*., 2015[11]	Spain	2	3 Malignant 2 Benign 1	Color analysis only - blue hard, green intermediate, and red soft	Olympus	No	-
He *et al*., 2015[9]	China	40	68 Malignant 42 Benign 26	Four grades: 1 point when over 80% of the section was green/yellow/red; 2 points when over 50% but <80% of the section was green/yellow/red; 3 points when over 50% but <80% of the section was blue; and 4 points when over 80% of the section was blue	Pentax	Yes; cutoff 32.07	Elastography grading score was higher in the malignant LN group than in the benign LN group (3.35±0.91 vs. 1.84±0.97, *P*=0.000)
Nakajima *et al*., 2015[7]	Japan	21 21 patients for *in vitro* elastography	49 Malignant 16 Benign 33 48 nodes for *in vitro* analysis (12 Malignant)	SAR: ratio of stiff area (blue color area) per LN area using the ImageJ 1.45 s software	Olympus	No	SAR was significantly greater for metastatic LNs (0.487 for metastatic nodes and 0.216 for benign nodes, *P*=0.0002) Using a cutoff value of 0.311 for SAR, the sensitivity and specificity for predicting metastatic disease were 0.81 and 0.85, respectively
Rozman *et al*., 2015[6]	Slovenia	33	80 Malignant 33 Benign 47	Strain ratio	Olympus	Yes; cutoff 8	Strain ratio values of ≥8 suggests the probability of malignant cause with an accuracy of 86.25%, sensitivity 88.24%, specificity 84.78%, PPV 81.08%, NPV 90.70%
Sun *et al*., 2017[12]	China	56	68 Malignant 35 Benign 33	Qualitative: 5 scores (score 1 - no blue; score 5 - predominantly blue) Quantitative: Mean gray value (0=all red, 255=all blue)	Pentax	No	For malignancy, RTE score 4-5: Sensitivity 85.7%, specificity 81.8% RTE gray score >192.32 Sensitivity 91.4%, specificity 72.3%
Korrungruang and Boonsarngsuk, 2017[14]	Thailand	72	120 Malignant 96 Benign 24	Three types Type 1: Predominantly nonblue (green, yellow and red) Type 2: Part blue, part nonblue (green, yellow, and red) Type 3: Predominantly blue	Olympus	Yes; cutoff 15.3	In diagnosing malignancy, non-Type 1 node had sensitivity, specificity, PPV and NPV to be 100%, 66.7%, 92.3% and 100%, respectively
Mittal *et al*., 2017[13]	India	1	1 Benign 1	Type 3	Olympus	Yes	Strain ratio - 22, Type 3 node in tuberculosis

SAR: Stiff area ratio, LNs: Lymph nodes, PPV: Positive predictive value, NPV: Negative predictive value, RTE: Real-time elastography

5 describes all blue.[12] In this method, nodes categorized as 4 or 5 have high likelihood of being malignant.

After systematic literature search, nine studies were identified for final review. Out of these, two were case reports[11,13] and rest seven were observational studies.[6-10,12,14] The first study on utilization of EBUS elastography was published in 2013 and elastography color dispersion was described ranging from 0 to 255 where 0 describes all blue while 255 describes all red.[10] Most studies have used different ways of elastography reporting as described previously. Whatever be the method of description, the basic principle and interpretation of the technique remain the same. Strain ratio measurement was described in 4 studies and variable cutoffs for malignancy ranging from 8 to 32 have been reported.[6,9,13,14] This suggests the inherent problem with the strain ratio measurement as the method has not been standardized.[13] Regarding qualitative

assessment, three studies reported Type 1–3 lymph nodes, one reported Grade 1–4, and one study reported 5 types of lymph nodes. Most studies described good sensitivity and specificity of EBUS elastography for differentiation of malignant and benign lymphadenopathy. One study analyzed the *in vitro* use of EBUS elastography on surgically resected lymph nodes.[7] The elastography image was saved and later on compared with histopathological picture with same dimensions. It was found that blue-colored areas on elastography had good correlation with its pathological counterpart in the form of malignant cell infiltration.

Although EBUS elastography appears a promising modality, it has limitations as a good diagnostic procedure. No elastography characteristics have been described to reliably differentiate between various benign causes of mediastinal lymphadenopathy, especially in high TB prevalence settings. In view of inherent similarity between various benign etiologies, in its present form, EBUS elastography is unlikely to be useful in this regard. Our cases describe early experience of EBUS elastography from India. Most studies on the utility of EBUS elastography are available from non-TB endemic areas and have small number of patients with TB. This tool may have different utility in TB endemic areas, and strain ratio cutoff may also vary. Increased lymph node hardness in tubercular nodes has also been described. Larger studies from TB endemic areas are required to answer this question and may help in better utilization of this newer modality.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Madan K, Mohan A, Ayub II, Jain D, Hadda V, Khilnani GC, *et al*. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchology Interv Pulmonol 2014;21:208-14.
2. Madan K, Dhungana A, Mohan A, Hadda V, Jain D, Arava S, *et al*. Conventional transbronchial needle aspiration versus endobronchial ultrasound-guided transbronchial needle aspiration, with or without rapid on-site evaluation, for the diagnosis of sarcoidosis: A Randomized Controlled Trial. J Bronchology Interv Pulmonol 2017;24:48-58.
3. Madan K, Ayub II, Mohan A, Jain D, Guleria R, Kabra SK, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in mediastinal lymphadenopathy. Indian J Pediatr 2015;82:378-80.
4. Ayub II, Mohan A, Madan K, Hadda V, Jain D, Khilnani GC, *et al*. Identification of specific EBUS sonographic characteristics for predicting benign mediastinal lymph nodes. Clin Respir J. 2016. doi: 10.1111/crj.12579. [Epub ahead of print].
5. Korrungruang P, Boonsarngsuk V. Endobronchial ultrasound elastography for the differentiation of benign and malignant lymph nodes-reply. Respirology 2017;22:1038.
6. Rozman A, Malovrh MM, Adamic K, Subic T, Kovac V, Flezar M, *et al*. Endobronchial ultrasound elastography strain ratio for mediastinal lymph node diagnosis. Radiol Oncol 2015;49:334-40.
7. Nakajima T, Inage T, Sata Y, Morimoto J, Tagawa T, Suzuki H, *et al*. Elastography for predicting and localizing nodal metastases during endobronchial ultrasound. Respiration 2015;90:499-506.
8. Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T. Endobronchial ultrasound elastography in the diagnosis of mediastinal and hilar lymph nodes. Jpn J Clin Oncol 2014;44:956-62.
9. He HY, Huang M, Zhu J, Ma H, Lyu XD. Endobronchial ultrasound elastography for diagnosing mediastinal and hilar lymph nodes. Chin Med J (Engl) 2015;128:2720-5.
10. Trosini-Désert V, Jeny F, Taillade L, Vignot S, Zribi H, Capron F, *et al*. Bronchial endoscopic ultrasound elastography: Preliminary feasibility data. Eur Respir J 2013;41:477-9.
11. Andreo García F, Centeno Clemente CÁ, Sanz Santos J, Barturen Barroso Á, Hernández Gallego A, Ruiz Manzano J, *et al*. Initial experience with real-time elastography using an ultrasound bronchoscope for the evaluation of mediastinal lymph nodes. Arch Bronconeumol 2015;51:e8-11.
12. Sun J, Zheng X, Mao X, Wang L, Xiong H, Herth FJF, *et al*. Endobronchial ultrasound elastography for evaluation of intrathoracic lymph nodes: A Pilot study. Respiration 2017;93:327-38.
13. Mittal S, Mohan A, Madan K. Endobronchial ultrasound elastography for the differentiation of benign and malignant lymph nodes. Respirology 2017;22:1037-8.
14. Korrungruang P, Boonsarngsuk V. Diagnostic value of endobronchial ultrasound elastography for the differentiation of benign and malignant intrathoracic lymph nodes. Respirology 2017;22:972-7.
15. Arcidiacono PG. Endoscopic ultrasound elastography. Gastroenterol Hepatol (N Y) 2012;8:48-67.