Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis.

Nesrin Kiral¹, Benan Caglayan¹, Banu Salepci¹, Elif Torun Parmaksiz¹, Ali Fidan¹,
Sevda Sener Comert¹, Dilek Yavuzer², Mualla Partal³

¹Dr. Lutfi Kirdar Kartal Training and Research Hospital Department of Chest Diseases, ²Dr. Lutfi Kirdar Kartal Training and Research Hospital Department of Pathology, ³Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Microbiology, Istanbul, Turkey

Abstract

Aims: Patients with suspected tuberculosis without pulmonary lesions and with intrathoracic lymphadenopathy often pose a diagnostic challenge. The aim of this study was to describe the diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in patients with isolated intrathoracic lymphadenopathy due to tuberculosis (TB). **Materials and methods:** Cases with tuberculous lymphadenitis (TBLA) as the final diagnosis were analysed among patients in whom EBUS-TBNA had been performed. All patients underwent routine clinical assessment and a CT scan prior to EBUS-TBNA. Demographic data, pathological findings, and microbiological results were recorded. All patients received 6-month antituberculous treatment, followed-up regularly and recovered both on clinical and radiological basis. **Results:** Forty-four patients were included. EBUS-TBNA diagnosed TB intrathoracic lymphadenopathy in 42 (95.4%) patients. In 2 patients, EBUS-TBNA was not able to confirm a diagnosis and additional procedures were required. Cytopathological findings alone revealed TB in 32 (72.7%) patients. One of the patients (2.2%) was smear positive while microbiological investigations provided a positive culture of TB in 22 (50%) patients. TB culture was positive in 10 of 12 patients in whom cytopathologic evaluation was not able to diagnose. Addition of mycobacterium culture to cytopathologic investigation has improved the diagnostic yield from 72.7% to 95.4%. **Conclusion:** EBUS-TBNA is a safe and effective first line investigation for evaluating isolated intrathoracic tuberculous lymphadenopathy. Addition of mycobacterium culture to cytopathologic investigation improves the sensitivity of EBUS-TBNA.

Keywords: bronchoscopy, endobronchial ultrasound, transbronchial needle aspiration, lymphadenopathy, tuberculosis

Introduction

Tuberculous (TB) is a major health problem with a high mortality rate in developing countries. Tuberculous lymphadenopathy (TBLA) is the most common form of extrapulmonary TB. The intrathoracic lymph nodes are frequently involved in endemic areas. The diagnosis may be difficult in the absence of accompanying parenchymal

involvement, the vast majority of such cases having negative sputum smear and cultures. Tomographical appearance of an adenopathy with a low-density center and peripheral rim enhancement does not confirm the diagnosis. Moreover, fungal infections or malignancy can also produce similar radiological abnormality. Mediastinoscopy, thoracotomy, or video-assisted thoracic surgery (VATS) may be warranted for definite diagnosis [1-3].

Being a simple, safe, and repeatable method, fine needle aspiration (FNA) is becoming increasingly popular in the diagnosis of extrapulmonary tuberculosis [4,5]. The diagnostic value of computed tomographic (CT) guided fine needle aspiration biopsies (FNAB) in mediastinal tuberculosis is 66% [6]. Gulati et al had seven culture positive cases out of 26 TB patients diagnosed by ultrasound (US) guided FNAB [2].

Received 24.03.2015 Accepted 20.06.2015

Med Ultrason

2015, Vol. 17, No 3, 333-338

Corresponding author: Nesrin Kiral, M.D

Kozyatagi Mah. Kocayol cad. Atilim Sitesi A
Blok 39/30, 34742 Kadikoy, Istanbul, TURKEY
Phone: +90 216 416 49 88
Gsm: +90 535 596 90 85, Fax: +90 216 442 18 84
E-mail: drnesrinkiral@yahoo.com

Fig 1. Distal tip of dedicated bronchoscope with the curved array transducer covered with a saline inflated balloon (a) and echogenic needle pushed out of the bronchoscope (b)

US has been increasingly incorporated into diagnostic and therapeutic modalities. US technology may be employed via a probe inserted through the working channel [radial probe endobronchial US (EBUS)] or incorporated into the distal end of the bronchoscope (convex probe EBUS), the latter allowing real-time biopsy. The convex probe EBUS bronchoscope, utilizes a fixed array of transducers aligned in a curvilinear pattern. This generates a 50° image parallel to the long axis of the bronchoscope. The use of a 7.5-MHz frequency transducer allows deeper tissue penetration. Using the water-filled balloon the image quality can be improved (fig 1). Power Doppler US differentiates the tissue from the vascular structure. US and the white-light bronchoscopic images can be display simultaneously [7,8].

Recently, development of EBUS has increased the validity of transbronchial needle aspiration (TBNA). Convex probe endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has a high sensitivity and diagnostic value in lung cancer and sarcoidosis; however, its utility in TB lymphadenitis has not been reported [7,9]. We undertook this study to assess the diagnostic yield of EBUS-TBNA in the evaluation of TBLA.

Material and methods

Patients

Between February 2009 and July 2013, 780 patients had undergone EBUS-TBNA in our Department for the study of radiographically detected hilar/mediastinal lymphadenopathy (adenopathy larger than 1 cm in short axis on CT). Out of 780 EBUS-TBNA cases, 736 were diagnosed with diseases other than tuberculosis by EBUS-TBNA itself or by additional diagnostic procedures. The records of 44 patients who were diagnosed as TBLA were retrospectively analysed. All the patients signed an informed consent before endoscopic procedure. Demo-

graphical data and results of cytopathological and microbiological analyses were recorded. The detection of caseating granulomatous reaction and/or direct identification of *Mycobacterium tuberculosis* by Ziehl-Neelson stain and/or growth in MGIT (Mycobacteria Growth Indicator Tube) system were considered as TBLA. Mediastinoscopy or other invasive procedures undertaken in the case of non-diagnostic EBUS-TBNA were recorded. Treatment results of all cases were also recorded.

Convex probe EBUS-guided TBNA

The bronchoscopy procedure was performed via oral route with the patient in supine position under local anesthesia and conscious sedation using intravenous midazolam. A 7.5-MHz BF-UC160F convex-probe bronchoscope and EU-C2000 processor (Olympus Optical Co, Tokyo, Japan) were used. The lymph nodes were classified according to the Mountain's regional lymph node classification system [10]. The dimensions of the lymph nodes seen on the convex probe-EBUS were recorded from archived US images. Although lymph nodes with a short axis greater than 1 cm at CT were included in the study, in presence of any lymph node with a short axis greater than 0.5 cm measured by EBUS, EBUS-guided TBNA was performed with real-time imaging (fig 2). TBNA was performed by using 22-gauge Olympus NA-201SX-4022 needle and power Doppler mode to avoid vascular injury. During the process, for every detected lymph node short and long axis diameters, station of the lymph node, and number of passes per patient and per lymph node were recorded in each patient.

The specimens obtained were immediately smeared on slides and fixed in 95% ethanol and flushed in 0.9% normal saline for pathological and microbiological assessment, respectively. There was not a pathologist on-site and the Ziehl-Neelsen smear reading was done in the microbiology laboratory after the bronchoscopy finished,

Fig 2. a) Right lower paratracheal lymph node. The tip of the needle is shown with an arrow. The echogenic view under the tip of the needle is an internal echo of the lymph node; b) The correlative CT image of the right lower paratracheal lymph node. LN – lymph node, VCS – vena cava superior

but on the same day. The specimens were stained with Ziehl-Neelsen stain and cultured MGIT media. The remaining aspirates were also expelled in alcohol for cell block analysis. Cytopathological findings revealing caseating granulomatous reaction or detection of acid-fast bacilli on smear or growth of mycobacterium tuberculosis in the MGIT system were considered to be TBLA. When EBUS-TBNA findings were non-diagnostic, the patients were submitted to mediastinoscopy.

All TB cases received anti-TB treatment and followed for at least 6 months.

Statistical analysis

The accuracy of EBUS-TBNA in the diagnosis of TBLA and contribution of smear and culture to the diagnosis were evaluated. Sensitivity of EBUS-TBNA and diagnostic values of cytopathological and microbiological tests were calculated using descriptive data.

Results

The mean age of study group (29 female and 15 male) was 50.55 ± 2.65 years (range between 11-82 years). The mean diameter of the short axis of lymph nodes based on EBUS was 2.01 ± 0.09 cm. The majority of aspirations were from subcarinal lymph nodes (station number 7). A total of 83 lymph nodes were sampled in 44 patients and 181 aspirations were applied. The number of aspirations was 2.2 per lymph node and 4.1 per patient (table I, fig 3).

Forty-two patients (95.4%) were diagnosed as TBLA by EBUS-TBNA via cytopathological (fig 4) and/or microbiological analysis. For two cases who had nondiagnostic EBUS-TBNA results, diagnosis of TB was reached by mediastinoscopy. No complications due to EBUS were seen. TB was diagnosed in 32 patients (72.7%) based on cytopathology. One of the cases had positive smears of the EBUS-guided aspirates. Mycobacterium tuberculosis was isolated in 22 cases (50%). Out of 12 cases with nondiagnostic cytopatho-

Fig 3. a) Right lower paratracheal lymph node (number 4R). The tip of the needle and internal echo of the lymph node are shown. b) Right lower paratracheal lymph node (number 4R). Bronchoscopic image (arrow shows the location of TBNA).

Fig 4. a) HE $\times$ 200. Cell block, necrotizing granuloma at the centre (arrow shows the necrosis); b) MGG $\times$ 200. EBUS-TBNA smear showing epithelioid granuloma (HE: Hematoxylin-eosin) (MGG: May Grünwald Giemsa)

logical analysis, 10 had positive TB cultures. One patient was TBNA material smear positive and was also cytopathologically diagnosed as TBLA. Considering culture results in addition to cytopathological analysis the diagnostic value of EBUS-TBNA increased from 72.7% to 95.4%. Consequently, the culture of TBNA material improved the diagnostic utility of EBUS-TBNA as much as 22.7%. The cytopathological and microbiological findings of lymph node stations are shown in Table II.

All patients received six-month antituberculous treatment, followed-up regularly and recovered both on a clinical and radiological basis.

Table I. Location, diameter and aspiration frequency of sampled lymph nodes

Lymph node station	Number of lymph nodes	Mean diameter (cm)	Mean passes per lymph node
2R	3	1.68 ± 0.70	2
2L	-	-	-
4R	25	1.83 ± 0.14	2.4
4L	4	0.93 ± 0.25	2
7	33	2.38 ± 0.15	2.3
10R	3	2.67 ± 0.33	1.3
10L	-	-	-
11R	8	1.69 ± 0.25	1.8
11L	7	1.71 ± 0.14	1.7
Total	83	2.01 ± 0.09	2.2

Table II. Distribution of lymph nodes diagnosed with cytopathology and/or tuberculous culture

Lymph node station	Lymph nodes diagnosed cytopathologically (n)	Lymph nodes with positive TB culture (n)	Lymph nodes with positive TB culture and nondiagnostic cytopathology (n)
2R	3	2	1
2L	—	—	—
4R	18	14	4
4L	2	3	1
7	20	19	8
10R	2	2	1
10L	—	—	—
11R	5	5	1
11L	3	3	2
Total	53	48	18

n-number

Discussions

The current study demonstrates a diagnostic value of 95.4% for EBUS-TBNA in intrathoracic TBLA. No complications were observed. Twenty two patients (50%) had positive cultures for *Mycobacterium tuberculosis*. Incorporating culture to cytopathological analysis the diagnostic rate increased from 72.7% to 95.4%.

TB is still a common universal health problem. TBLA accounts for about 30-40% of the cases and is one of the most frequent causes of lymphadenopathy [11]. Fine needle aspiration is a simple, non-invasive alternative to excisional biopsy [5]. The diagnosis is confirmed by the recognition of epithelioid histiocyte granulomas with or without multinucleate giant cells and caseation necrosis [11]. Acid fast staining of the aspirates seem to increase the diagnostic rate [12]. The prevalence of acid resistant bacilli in smears prepared using the Ziehl-Neelsen technique has been reported to vary from 0 to 76.4% [11,13]. Nataraj et al found that culture positivity was significantly higher than smear positivity [4]. Cultures of fine needle aspirates are thought to be a more specific additional tool to increase sensitivity in TBLA evaluation [14]. Our findings suggest that using cultures as an adjunct to cytopathological analysis the diagnostic rate increase from 72.7% to 95.4%. Bronchoscopy and sputum culture have a limited role in diagnosing isolated intrathoracic TBLA. Bilaçeroğlu et al found the diagnostic yield of cultures of conventional TBFNA to be 27 % (17/63) [1]. Mediastinoscopy may be employed; however, it is more invasive, requires general anesthesia and carries 1-2% morbidity [3,15]. Another disadvantage is that posterior subcarinal and hilar lymph nodes cannot be accessed. Anterior mediastinoscopy or thoracotomy may be required to establish their diagnosis [3]. Farrow et al obtained 14/24 culture positivity by mediastinoscopy [16].

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has recently emerged as an important tool in diagnosing TBLA. The diagnostic yield was found to be 90-93% [17,18]. Songür et al sampled celiac lymph nodes by EUS-FNA and detected acid-fast bacilli [19]. EUS-FNA cannot reach right paratracheal or hilar lymph nodes, which are commonly involved in TB. In a study, *Mycobacterium tuberculosis* culture positivity was found to be 21% by EUS [18].

Currently, EBUS-TBNA is an important alternative of mediastinoscopy in diagnosis of granulomatous intrathoracic lymphadenopathy. It is well-tolerated outpatient procedure, providing access to intrathoracic and hilar lymph nodes as well as enabling bronchial washing [7,20]. It allows higher smear and culture positivity compared to conventional TBNA [21]. The isolation of the agent allows susceptibility testing [20]. Due to the novelty of this method, there are limited studies on this subject.

EBUS samples that demonstrate necrotic granulomas or necrosis are more likely to have positive TB cultures [20,22]. Navani et al observed 47% culture positivity through EBUS-TBNA and concluded that the bacillary load was higher in necrotising lesions, thereby increasing culture positivity in these lymph nodes [20]. According to another study, the cultures for mycobacterium TB were positive in 49% and maximum positivity was seen in necrotic material [22]. In our study, necrosis was found in 18.1% of cases with culture positivity.

It is well documented that EBUS-TBNA is an important tool in staging lung cancer [9,23]. The complications reported are no more than few case reports. Symptomatic bacteremia was observed in one patient [20], and a case with mediastinal-esophageal fistulae following EUS-FNA of subcarinal lymph node with a 22 gauge needle was described [24]. A non-small cell lung cancer patient who had experienced mediastinitis

following EUS guided aspiration of a necrotic subcarinal lymph node has been reported in another study [25]. The fact that no major complications were encountered in our study supports the idea that EBUS-TBNA is a safe procedure.

One limitation of our study is that the analysis is retrospective and the patient population is small. Prospective studies conducted in larger populations evaluating microbiological and cytological results of EBUS-TBNA are required.

Conclusions

EBUS-TBNA is a safe and reliable method with a high accuracy in diagnosing TBLA. The diagnostic yield may be increased by the addition of mycobacterium cultures as a routine laboratory examination. Therefore, we emphasize the need for incorporating mycobacterium cultures in the evaluation of intrathoracic lymph nodes with EBUS-TBNA.

Conflict of interest: none

References

1. Bilaçeroğlu S, Günel O, Eriş N, Çağırıcı U, Mehta AC. Transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. *Chest* 2004; 126: 259-267.
2. Gulati M, Venkataramu NK, Gupta S, et al. Ultrasound guided fine needle aspiration biopsy in mediastinal tuberculosis. *Int J Tuberc Lung Dis* 2000; 4: 1164-1168.
3. Aksel N, Tavusbay NA, Çakan A, Özsöz A. Our cases of tuberculous lymphadenitis. *Türkiye Klinikleri Arch Lung* 2005; 6: 30-33.
4. Nataraj G, Kurup S, Pandit A, Mehta P. Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. *J Postgrad Med* 2002; 48: 113-116.
5. Khan FY. Clinical pattern of tuberculous adenitis in Qatar: experience with 35 patients. *Scand J Infect Dis* 2009; 41: 128-134.
6. Khan J, Akhtar M, von Sinner WN, Bouchama A, Bazarbashi M. CT-guided fine needle aspiration biopsy in the diagnosis of mediastinal tuberculosis. *Chest* 1994; 106: 1329-1332.
7. Caglayan B, Salepçi B, Fidan A, et al. Sensitivity of convex probe endobronchial sonographically guided transbronchial needle aspiration in the diagnosis of granulomatous mediastinal lymphadenitis. *J Ultrasound Med* 2011; 30: 1683-1689.
8. Sheski FD, Mathur PN. Endobronchial ultrasound. *Chest* 2008; 133: 264-270.
9. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer* 2009; 45: 1389-1396.
10. Mountain CF, Dressler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997; 111: 1718-1723.
11. Mittal P, Handa U, Mohan H, Gupta V. Comparative evaluation of fine needle aspiration cytology, culture, and PCR in diagnosis of tuberculous lymphadenitis. *Diagn Cytopathol* 2011; 39: 822-826.
12. Bezabih M, Mariam DW, Selassie SG. Fine needle aspiration cytology of suspected tuberculous lymphadenitis. *Cytopathology* 2002; 13: 284-290.
13. Ersöz C, Polat A, Serin MS, Soylu L, Demircan O. Fine needle aspiration (FNA) cytology in tuberculous lymphadenitis. *Cytopathology* 1998; 9: 201-207.
14. Kishore Reddy VC, Aparna S, Prasad CE, et al. Mycobacterial culture of fine needle aspirate - A useful tool in diagnosing tuberculous lymphadenitis. *Indian J Med Microbiol* 2008; 26: 259-261.
15. Sayar A, Ölçmen A, Metin M, Güleç H, Demir A, Ölçmen M. Role of mediastinoscopy in intrathoracic tuberculous lymphadenitis. *Asian Cardiovasc Thorac Ann* 2000; 8: 253-255.
16. Farrow PR, Jones DA, Stanley PJ, Bailey JS, Wales JM, Cookson JB. Thoracic lymphadenopathy in Asians resident in the United Kingdom: role of mediastinoscopy in initial diagnosis. *Thorax* 1985; 40: 121-124.
17. Puri R, Vilman P, Sud R, et al. Endoscopic ultrasound-guided fine-needle aspiration cytology in the evaluation of suspected tuberculosis in patients with isolated mediastinal lymphadenopathy. *Endoscopy* 2010; 42: 462-467.
18. Song HJ, Park YS, Seo DW, et al. Diagnosis of mediastinal tuberculosis by using EUS-guided needle sampling in a geographic region with an intermediate tuberculosis burden. *Gastrointest Endosc* 2010; 71: 1307-1313.
19. Songür Y, Songür N, Ciriş M, et al. Endoscopic ultrasound-guided fine needle aspiration cytology of tuberculous lymphadenitis: demonstration of acid-fast bacilli. *Cytopathology* 2010; 21: 64-65.
20. Navani N, Molyneaux PL, Breen RA, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. *Thorax* 2011; 66: 889-893.
21. Mehta MR, Connell DW, Wickremasinghe MI, Kon OM. The use of thoracic computed tomography scanning and EBUS-TBNA to diagnose tuberculosis of the central nervous system: two case reports. *Eur Respir Rev* 2010; 19: 345-347.
22. Gupta SK, Chugh TD, Sheikh ZA, al-Rubah NA. Cytodiagnosis of tuberculous lymphadenitis. A correlative study with microbiologic examination. *Acta Cytol* 1993; 37: 329-332.
23. Alataş F, Dündar E, Yıldırım H, Metintaş M, Akdoğan Ak G. Role of real-time endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis and mediastinal staging of lung cancer. *Türkiye Klinikleri J Med Sci* 2012; 32: 407-414.

24. Von Bartheld MB, van Kralingen KW, Veenendaal RA, Willems LN, Rabe KF, Annema JT. Mediastinal-esophageal fistulae after EUS-FNA of tuberculosis of the mediastinum. *Gastrointest Endosc* 2010; 71: 210-212.
25. Aerts JG, Kloover J, Los J, van der Heijden O, Janssens A, Tournoy KG. EUS-FNA of enlarged necrotic lymph nodes may cause infectious mediastinitis. *J Thorac Oncol* 2008; 3: 1191-1193.