Original Article

GeneXpert Analysis Combined with EBUS-TBNA Increased Diagnostic Yield of TB Mediastinal Lymphadenitis

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Objective: To evaluate yield of GeneXpert combined endobronchial ultrasound with transbronchial needle aspiration [EBUS-TBNA] for detect mediastinal TB lymphadenitis in suspected TB patients.

Materials and Methods: Suspected mediastinal TB lymphadenitis patients who visited Central Chest Institute of Thailand between October 2013 and September 2014 were included. EBUS-TBNA was done. They were assessed by direct smear, liquid culture, GeneXpert, and tissue from node. Mediastinoscopy and/or clinical resolving were followed.

Results: Thirty suspected mediastinal TB lymphadenitis patients who needed EBUS-TBNA were included. Six of them had no final diagnosis as they denied to be investigated, so only 24 patients were studied. Definite diagnosis were 12 TB, 2 sarcoidosis, 8 carcinoma, 1 Hodgkin lymphoma, 1 substernal goiter. Four of 12 TB patients showed pattern of granulomatous inflammation/caseous granuloma in EBUS-TBNA, two of four granulomatous inflammation/caseous granuloma samples were positive in GeneXpert. GeneXpert was positive in four patients of 12 TB patients (33%). GeneXpert combined with EBUS-TBNA was positive in five of 12 TB patients. No sample was positive on direct smear or liquid cultures.

Conclusion: GeneXpert combined with EBUS-TBNA has more benefits than node direct smear and standard culture.

Keywords: GeneXpert, BUS-TBNA, TB lymphadenitis

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Tuberculosis [TB] is a main problem in Thailand. Some patients who had TB lymphadenitis may be progressed to TB lung. Most common of TB lymphadenitis is cervical, inguinal, mediastinal, and axilla. Definite diagnosis of TB lymph node [LN] is LN biopsy. Sometimes, it is difficult to diagnosis because the LN position is difficult to access such as mediastinal lymphadenitis.

Endobronchial ultrasound with transbronchial needle aspiration [EBUS-TBNA] is a new technology to work up mediastinal lymphadenopathy. It is the best way to diagnose malignancy. Result of EBUS-TBNA for mediastinal TB lymphadenitis is controversial.

Materials and Methods

Patients

The present study was conducted between October 2013 and September 2014 at the Bronchoscopy unit of Central Chest Institute of Thailand. Patients with suspected mediastinal TB lymphadenitis were enrolled. Suspected mediastinal TB lymphadenitis was defined by mediastinal lymphadenopathy more than 1 cm by CT contrast media with no cervical lymphadenopathy, no positive sputum direct smear, and no pattern of suspected lung cancer such as mass. Thirty patients were included for the present study. The Ethical Committee of the Central Chest Institute of Thailand approved the protocol. Informed consents were obtained from all patients enrolled in the present study.

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GeneXpert[1-4]

Aspiration specimens were inoculated to MB/BacT liquid medium (bioMérieux, Marcy l'Etoile, France) for growth detection. The remaining specimens were processed by GeneXpert to detect the rpoB gene. Bidirectional sequencing was performed on the 81-bp rpoB core region of culture isolates in all rifampin-resistant and discordant strains with forward (CGT GGA GGC GAT CAC ACC GCA GAC) and reverse (AGC TCC AGC CCG GCA CGC TCA CGT) primers with the use of the BigDye Terminator Cycle Sequencing kit, according to the manufacturer's recommendations, in a 3130xl Genetic Analyzer (Applied Biosystems).

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EBUS-TBNA[5-7]

EBUS-TBNA was performed with a flexible ultrasonic puncture bronchoscope with a linear scanning transducer (CP-EBUS, XBF-UC260F-OL8; Olympus; Tokyo, Japan)[4]. Local anesthesia (lidocaine nebulizer) was applied. The procedure was performed under light sedation with pethidine. After full inspection of the mediastinal LNs accessible by EBUS-TBNA, target nodal station was aspirated three times with a dedicated 22-gauge needle (NA-201SX-4022; Olympus).

The aspirate was expelled onto glass slides, smeared, and immediately fixed with 95% alcohol for cytology and not fixed with 95% alcohol for direct smear of TB. Tissue cores obtained by EBUS-TBNA were put into a solution of 10% neutral-buffered formalin. The remaining aspiration specimens were collected for real time-polymerase chain reaction [PCR] (GeneXpert) and liquid culture of TB.

Definite diagnosis of TB lymphadenopathy defined by lymphadenopathy was the positive direct smear or positive liquid culture of TB or caseous granuloma and/or clinical/CXR improvement (decreased size of LN) after antituberculosis treatment.

Statistical analysis

Descriptive analysis and diagnostic test such as sensitivity, specificity, and accuracy were calculated.

Results

Of the 30 suspected mediastinal TB lymphadenopathy, 24 patients were included in the present study. All were performed under EBUS-TBNA. Definite diagnoses are shown in Table 1. No final diagnosis was found in six patients because of denied further work up. Details of 12 definite diagnosis of TB is shown in Table 2. Mediastinoscopy was done in seven patients. Results of mediastinoscopy is shown in Table 3.

The results show 12 definite diagnosis of TB. GeneXpert was positive in four of 12 TB lymphadenitis patients. After antituberculous treatment, the four positive GeneXpert patients were decreased in size of LN. All TB lymphadenitis patients were negative direct smear and liquid culture of TB. Two of four positive GeneXpert samples showed granulomatous inflammation/caseous granuloma. The others showed non-diagnostic. Tissue specimens showed three granulomatous inflammation and one caseous granuloma. Two of the three granulomatous inflammation patients were diagnosed TB and another one was diagnosed sarcoidosis by mediastinoscopy and no response to antituberculosus drugs. One of two TB induced granulomatous inflammation cases was positive GeneXpert and another one was diagnosed by clinical response. One patient who had caseous granuloma was negative in all GeneXpet, liquid culture, and direct smear. After antituberculous treatment, all TB lymphadenitis decreased nodes size. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA specimen was 25%, 94%, 75%, 65%, and 66%, respectively. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of combination in EBUS-TBNA and GeneXpert was 41%, 94%, 83%, 70%, and 73%, respectively.

Table 1. Definite diagnosis of lymphadenopathy

Definite diagnosis	Number of patients
Tuberculosis	12
Sarcoidosis	2
Carcinoma	8
Hodgkin lymphoma	1
Substenal goiter	1
No definite diagnosis	6

Discussion

TB Lymphadenitis is difficult to diagnose, especially mediastinal lymphadenopathy. EBUS TBNA has benefit in diagnosing malignancy. EBUS-TBNA for TB Lymphadenitis is controversial because there is no better investigation tool.

WHO recommend GeneXpert MTB/RIF System to help diagnose extrapulmonary TB. A previous study(4) showed sensitivity 70.6% and specificity 100% in TB lymphadenitis using GeneXpert in all case. A previous multicenter study in Australia[8] found sensitivity of EBUS-TBNA for microbiologically confirmed mediastinal TB lymphadenitis to be at 62% (24/39) and specificity at 100%. Another study[9] showed sensitivity, specificity, positive predictive value, and negative predictive value of TB-PCR for TB lymphadenopathy by EBUS-TBNA at 56%, 100%, 100%, and 81%.

The present study had a small sample size for calculating sensitivity and specificity. The result showed that GenXpert increased positive predictive value and accuracy at 75% (three out of four granulomatous inflammation and caseous granuloma) and 65% by EBUS-TBNA to 83% (five out of six granulomatous inflammation/caseous granuloma combined with positive GeneXpert) and 73%.

Table 2. Description data in TB lymphadenitis

Case No.	Age/sex	Position, size of node	EBUS cytology	EBUS pathology	Node AFB	Node culture	GeneXpert	Response
3	26/F	4R, 1.8	Non-diagnostic		Negative	Negative	MTB	Anti TB drug: response
5	69/M	4R, 1.6	Negative	Poorly formed granuloma	Negative	No growth	MTB	Anti TB: response (HIV positive)
6	53/F	4R, 1.7	Negative	Negative	Negative	No growth	No detection	After follow-up, positive cervical lymphadenopathy: granulomatous lymphadenopathy Response of anti TB treatment
12	64/M	4R, 1.2	Negative	Negative	Negative	No growth	MTB	RML pneumonia TBB: non-caseous granulomatous inflammation Response to anti TB drug
16	32/F	4L, 1.5	Non-diagnostic	Necrotic tissue	Negative	No growth	No detect	Lobectomy: necrotizing granuloma No relapse
18	32/F	7, 2.2	Non-diagnostic	Non-diagnostic	Negative	No growth	No detection	Mediastinoscopy: granulomatous lymphadenitis Response to anti TB drug
19		7, 1.5		Caseous granuloma	Negative	No growth	MTB	Response to anti TB
20	62/M	7, 1.2	Negative	Negative	Negative	No growth	No detection	TBB: LUL lesion: non-caseous granuloma Response to anti TB
21	36/M	4L, 1.5	Negative	Granulomatous inflammation	Negative	No growth	No detection	TBB: RLL lesion: necrotizing granulomatous granulation Response to anti TB
22	81/M	7, 1.2	Negative	Negative	Negative	No growth	No detection	
27	56/M	10R, 1.0	Non-diagnostic	Non-diagnostic	Negative	No growth	No detection	Response to treatment
30	53/F	4R, 1.2	Non-diagnostic	Non-diagnostic	Negative	No growth	No detection	Mediastinoscopy: non-caseous granulomatous lymphadenitis

EBUS = endobronchial ultrasound; AFB = acid fast bacilli; M = male; F = female; MTB = Mycobacterium tuberculosis; TB = tuberculosis; TBB = transbronchial biopsy; RML = right middle lobe; LUL = left upper lung

Table 3. Results of mediastinoscopy

Case No.	Age/sex	Position, size of node	EBUS cytology	EBUS pathology	Node AFB	Node culture	GeneXpert	Mediastinoscopy
4	33/F	4R, 1.6	Granulomatous inflammation	Non-diagnostic	Negative	Negative	No detect	Non-caseous granuloma Anti TB: no response Dx sarcoidosis Response to steroid
13	34/M	4R, 1.2	Negative	Negative	Negative	Negative	No detect	Reactive node
14	23/F	4R, 1.0	Negative	Negative	Negative	Negative	No detect	Lymphoma
18	32/F	7, 2.2	Non-diagnostic	Non-diagnostic	Negative	No growth	No detect	Mediastinoscopy: granulomatous lymphadenitis Response to anti TB drug
25	30/F	10R, 1.4	Non-diagnostic	Non-diagnostic	Negative	No growth	No detect	Atypical cell, suspicious of malignancy
29	51/F	4R, 1.4	Non-diagnostic	Non-diagnostic	Negative	No growth	No detect	Non-caseous granulomatous lymphadenitis No response to anti TB Dx sarcoidosis
30	53/F	4R, 1.2	Non-diagnostic	Non-diagnostic	Negative	No growth	No detect	Mediastinoscopy: non-caseous granulomatous lymhadenitis Response to anti TB drug

EBUS = endobronchial ultrasound; AFB = acid fast bacilli; M = male; F = female; TB = tuberculosis

Diagnosis of Sarcoidosis was done by mediastinoscopy or after ruling out TB due to its high prevalence in Thailand. A previous study[10] had a better yield of EBUS-TBNA in stage 4 than at other stage.

Standard diagnosis of TB mediastinal lymphadenitis is done using caseous granuloma by tissue pathology. EBUS-TBNA and GeneXpert are not adequate to replace standard diagnosis.

The present study found that combination of EBUS-TBNA and GeneXpert was better than EBUS-TBNA alone.

What is already known on this topic?

Benefit of combination in EBUS-TBNA and GeneXpert in TB mediastinal lymphadenopathy.

What this study adds?

Combination in EBUS-TBNA and GeneXpert was better than EBUS-TBNA alone.

Potential conflicts of interest

The authors declare no conflict of interest.

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