Role of transbronchial needle aspiration in patients with thoracic lymphadenopathy on CT scan

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Abstract: Context: Transbronchial needle aspiration (TBNA) is a method in which an aspirating needle is used to obtain diagnostic samples from a peribronchial or submucosal lesion through a rigid [1] or flexible bronchoscope [2]. Though it is a very useful bronchoscopic technique it still remains underutilized [3]. Aims: This study was done to evaluate the sensitivity, complication rates and factors affecting the outcome of TBNA. Settings and Design: Prospective trial of fifty two patients with mediastinal lymphadenopathy on CT scan attending Respiratory Diseases Clinic of Jawaharlal Nehru Medical College Hospital. Methods and Material: We analyzed the outcome of TBNA in fifty two patients who underwent TBNA between 2010 and 2012. Sensitivity of TBNA was calculated and factors affecting the TBNA results were analyzed. Statistical analysis used:Chi square test was used for analyzing the factors affecting TBNA results. SPSS Statistics 17.0 was used for analysis. Results: The overall sensitivity of TBNA was found to be 59.6% and it was the only diagnostic technique in 47.6% of the patients. Factors associated with diagnostic acquisition of samples were lymph node size more than 1.5 cm and the presence of indirect signs on bronchoscopy. Conclusions: The sensitivity of TBNA is high in malignant mediastinal lymphadenopathy. Complications occurred in four patients who had self limited bleeding at the site of puncture which healed spontaneously. Important factors predicting the outcome of TBNA are lymph node size and the presence of indirect signs on bronchoscopy. We would recommend this procedure for detection of metastatic lymph nodes in patients with lung cancer and also for mediastinal tubercular lymphadenopathy where diagnosis could not be achieved by less invasive methods.

Keywords: Transbronchial Needle Aspiration, Mediastinal Lymphadenopathy

1. Introduction

Transbronchial needle aspiration (TBNA) is a very useful method for obtaining diagnostic material from mediastinal lymph nodes[a] but still it remains underutilized[4]. The major reasons for underutilization of TBNA are suboptimal bronchoscopy technique, lack of technician support, lack of cytopathology support or the belief that TBNA is not useful [3]. This study was done to evaluate the role of TBNA in patients with enlarged mediastinal lymph nodes on CT scan in a tertiary care hospital in North India.

2. Material and Methods

The study was conducted at Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh. It was a prospective study involving 52 patients with mediastinal lymphadenopathy on CT scan who presented to JNMCH from November 2010 to November 2012.

2.1. Patient Inclusion Criteria

Patients coming to Department of TB and Respiratory Diseases, JNMCH who were found to have mediastinal lymphadenopathy on CT scan.

2.2. Patient Exclusion Criteria

- Patients having allergy to radiological contrast media and those who could not undergo CT scan for any reason.
- Patients unable to undergo bronchoscopy or those who did not give consent for bronchoscopy.
- Patients whose diagnosis could not finally be reached after using all available investigations or due to loss to follow up.
- Patients with lesion in the tracheo bronchial tract at the puncture point at the time of TBNA.

The patients were followed until a diagnosis could be made by appropriate investigations and clinico radiologic follow up.

2.3. Tbna Procedure

Prior to the TBNA procedure, patients were informed about the possible risks and complications of the procedure and informed consent was taken. Mediastinal or hilar adenopathies were identified prior to bronchoscopy on the basis of chest CT.

Topical 2% lignocaine was used for local anaesthesia by nebulization. Lignocaine jelly was used for nasal anaesthesia and providing lubrication during insertion of the bronchoscope. Nasal route was used for introduction of the bronchoscope with the patient in supine decubitus position.

TBNA of selected mediastinal adenopathies stations was performed before exploration of the bronchial tree while avoiding bronchoscopic aspiration or contamination with secretions, as far as possible. The insertion point was determined after a careful analysis of thoracic CT and following previous recommendations by other authors[5, 6]. TBNA was carried out at the most accessible and largest adenopathy when there were several lymph node enlargements. No cytopathologist was not present during the procedure for microscopic evaluation of the cytology.

Flexible bronchoscopy was not repeated when the first procedure failed to achieve a diagnosis. TBNA specimens were prepared by direct smear technique. The needle content was coated on a glass slide and fixed with 95% alcohol solution for cytological examination.

2.4. Data Interpretation and Analysis

All samples with high lymphoid cellularity (at least 30%) suggesting a lymph node puncture or the presence of many neoplastic cells or cytological findings that allowed for a specific diagnosis were considered "Adequate samples"[7]. Samples with atypias or dubious, bloody, mucousy, or tracheobronchial wall cellularity were considered "non-adequate". Patients in whom TBNA performed in more than one lymph node station, the most adequate diagnosis was selected.

Diagnosis of malignancy was defined by the presence of malignant cells in cytologic specimens. Tuberculosis was diagnosed if the specimen revealed granulomatous inflammatory changes with apparent necrosis or acid-fast organisms identified in smears, with Mycobacterium tuberculosis growth in Lowenstein cultures and/or clinical-radiologic recovery with standard antituberculous therapy.

2.5. True Positive (TP)

Adequate samples that allowed a specific diagnosis to be made were considered as True Positive. True positives were not further evaluated owing to the high specificity ascribed to TBNA by previous studies; the occurrence of false positives is very rare.

2.6. False Negative (FN)

All non adequate samples and those adequate samples which could not be confirmed by surgical techniques or follow up were considered as False Negative.

2.7. Calculations and Statistical Analysis

Qualitative variables were reported as absolute frequencies and percentages and numeric variables were reported as median and range. The sensitivity (Se) was calculated according to the standard definitions –

Sensitivity = TP / (TP + FN)

Factors affecting the acquisition of diagnostic samples were calculated from the data obtained. Comparison of discrete variables was performed by applying Chi Square Test. A p value of less than 0.05 was considered significant. Analyses were performed with SPSS, version 17.0 (SPSS, Chicago, IL, USA).

3. Results

Fifty seven patients were taken up for the study. Five patients were withdrawn from the study due to failure to make a final diagnosis and loss to follow up (8.8%).

The male to female ratio in the study was found to be 44:8 i.e. 85% were males and 15% were females.

The age and sex distribution of patients are shown in Table 1.

A total of 129 lymph nodes were found enlarged on CT scan. Only those lymph nodes which were accessible to bronchoscopy are mentioned in the observations [Table 2].

Fifty seven TBNA's were performed in different lymph node stations. Forty seven TBNA's were performed at 1 station and 5 TBNA's were performed at 2 stations [Table 3].

Table 1. Age and sex distribution of patients according to diagnosis

Pathology	Patients n (%)	Median Age in years	Male, n (%)	Female n (%)

		(range)		
Non-small cell lung carcinoma	42(80.8)	50(27-70)	36(85.7)	6(14.3)
Small cell lung carcinoma	6(11.5)	65(50-70)	5(83.3)	1(16.7)
Tuberculosis	4(7.7)	24.5(14-50)	3(75)	1(25)
Total	52	50(14-70)	44(84.6)	8(15.4)

Table 2. *Table showing the total lymph nodes examined according to pathology*

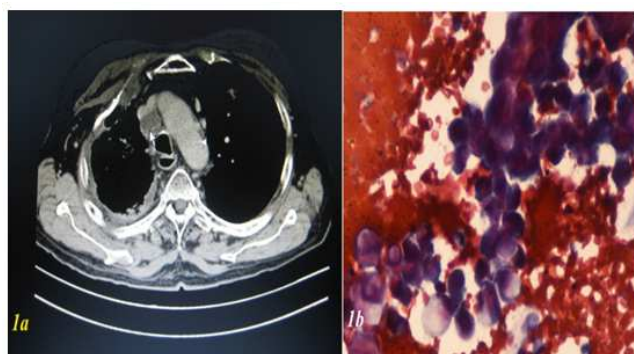| Lymph nodes	RP	LP	AP	SC	H	Total
Non-small cell lung carcinoma	33	12	25	32	4	106
Small cell lung carcinoma	5	2	3	5	1	16
Tuberculosis	2	1	1	3	0	7
Total	40	15	29	40	5	129

RP –Right paratracheal, LP-Left paratracheal, AP-Aortico pulmonary, SC-Subcarinal, H-Hilar

Table 3. *Characteristics of the mediastinal and hilar adenopathies*

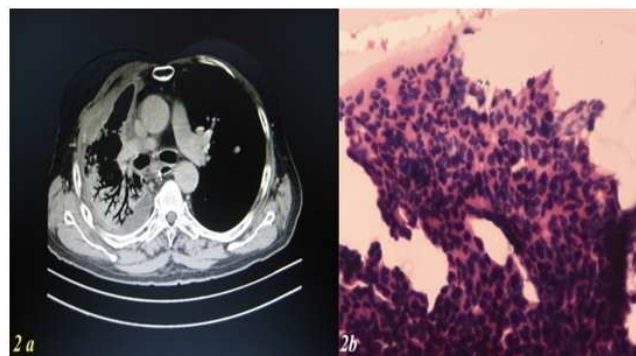| Pathology	Lymph nodes examined	Lymph node stations punctured per patient	Passes*	Lymph node size, mm*
Non-small cell lung carcinoma	106	1(1-2)	129	16 (9-35)
Small cell lung carcinoma	16	1(1-2)	19	17 (12-31)
Tuberculosis	7	1	20	15 (13-16)
Total	**129**	**1(1-2)**	**168**	**16(9-35)**

*Data presented as median (range)

Adequate samples were obtained in 33 of the 42 i.e. 78.6% non small cell lung cancer patients. Among these patients, diagnosis could be established by TBNA for 25 patients (59.5 %). Thus all patients whose TBNA was negative were classified as false negatives. [Figure 1a and b]
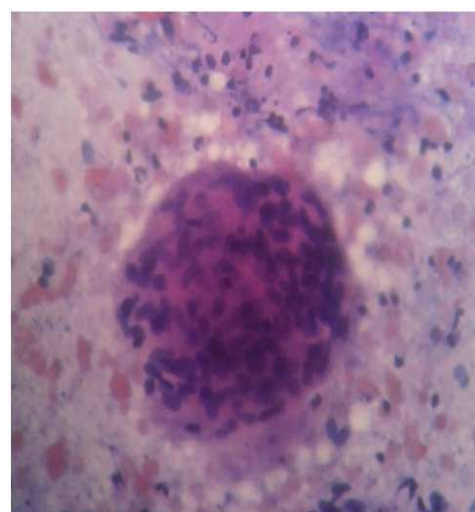

Figure 1a. *CT scan of a patient showing enlarged right paratracheal lymph node.* ***Figure 1b.*** *Mucin secreating adenocarcinoma lung metastatic to lymph node: FNA smear shows neoplastic cells with eccentric nuclei and evidence of mucin production (H & E stain, X 500)*

Adequate samples could be obtained for 5 of the 6 small cell lung cancer patients. Diagnosis was achieved by TBNA in 4 of these patients. [Figure 2a and b]

Figure 2a. *CT scan of a patient showing enlarged subcarinal lymph node.* ***Figure 2b.*** *Metastatic small cell carcinoma lung: FNA smear shows fragment of oat cells with extremely scant cytoplasm, hyperchomatic nuclei with characterstic nuclear moulding and faceting (H & E stain, X 500)*

Adequate samples were obtained in 2 of the 4 patients of tuberculosis which suggested a granulomatous inflammation with necrosis. Ziehl Neelsen (ZN) staining in one of these patients was positive for Acid Fast Bacilli (AFB) and the other showed growth of Mycobacterium tuberculosis on Lowenstein Jensen Medium (LJ Medium). [Figure 3]

Figure 3. *Tuberculosis: FNA smear with well formed epithelioid cell granuloma (H & E stain, X 500)*

The overall sensitivity of TBNA was found to be 59.6% and it was the only diagnostic technique in 47.6% of the patients. [Table 4]

Table 4. *Table showing number of adequate and diagnostic TBNA samples obtained, sensitivity of TBNA and number of patients in whom TBNA was a unique diagnostic technique*

Pathology	Number of adequate samples,	Number of diagnostic TBNA's, n	Se (%)	Unique diagnostic, n (%)

	n (%)	(%)		
Non-small cell lung carcinoma	33(78.6)	25(59.5)	59.5	20(47.6)
Small cell lung carcinoma	5(83.3)	4(66.7)	66.7	4(66.7)
Tuberculosis	2(50)	2(50)	50.0	2(50)
Total	39(75)	31(59.6)	59.6	26(50)

Se – Sensitivity, Sp – Specificity, PPV Positive Predictive Value, NPV – Negative Predictive Value

Univariate analysis was done for factors affecting the TBNA results. Comparison of proportions was done using the Chi Square Test.

A p value of less than 0.05 was considered significant. The analysis showed that the factors associated with diagnostic acquisition of samples were lymph node size more than 1.5 cm and the presence of indirect signs on bronchoscopy [Table 5].

Table 5. *Table showing the univariate analysis of the factors associated with the acquisition of diagnostic samples on TBNA*

Factor	Diagnostic samples	p value
Age		
Less than 60 years	21/33 (63.6%)	0.436
60 years or more	10/19 (52.6%)	
Sex		
Male	28/44 (63.6%)	0.166
Female	3/8 (37.5%)	
Lymph node station		
Right paratracheal	13/22 (59.1%)	
Left paratracheal	3/4 (75%)	0.974
Subcarinal	11/19 (57.9%)	
Hilar	1/2 (50%)	
Combination of 2	3/5 (60%)	
Lymph node size		
Less than 1.5 cm	7/20 (35%)	0.004
1.5 cm or more	24/32 (75%)	
Type of disease		
Benign	2/4 (50%)	0.683
Malignant	29/48 (60.4%)	
Small and Non small cell lung carcinoma		
Non-small cell lung carcinoma	25/42 (59.5%)	0.738
Small cell lung carcinoma	4/6 (66.7%)	
Indirect signs		
Yes	19/24 (79.2%)	0.008
No	12/28 (42.9%)	

No major complication occurred in any of the patients during the TBNA procedure. Four patients (7.7%) had self limited bleeding at the site of puncture which healed spontaneously.

4. Discussion

TBNA is a very important tool in the armamentarium of a Respiratory Physician but the acceptance and yield vary widely [3]. The major use of TBNA lies in the detection of malignant mediastinal lymphadenopathy for accurate staging of lung cancer where it may obviate the need for a mediastinoscopy or mediastinotomy. It is also helpful in the diagnosis of benign diseases like tuberculosis and sarcoidosis though the yield remains less than that for malignant neoplasms.

The study was carried out in 52 patients who had evidence of mediastinal lymphadenopathy on CT scan. The lymph nodes for TBNA were selected after review of CT chest and the largest and most accessible lymphadenopathy was selected for TBNA. False positive TBNA results were avoided by sampling the mediastinal nodes before exploration of the bronchial tree and excluding the cases that had a lesion on the tracheo bronchial tract at the point of puncture. Thus all positive results were taken as true positive and not investigated further.

The overall sensitivity of TBNA in our study was 59.6%. Reported sensitivity of TBNA has varied widely in individual studies. In 1984, Shure and Fedullo had reported a sensitivity of 15% in 110 patients with bronchogenic carcinoma[8]. None of the twenty four patients with benign disease had positive needle aspirates. However, bronchogenic carcinoma was suspected and TBNA done on the basis of an abnormal chest roentgenogram. In 1986, Schenk et al. reported a sensitivity of 94% in 88 patients of bronchogenic carcinoma[9]. In this study CT scan was used for selecting the adenopathy to be sampled by TBNA. They also reported 2 false positive TBNA in this study, one positive aspirate had been contaminated by tracheal debris. In our study, we had minimized such false positives performing TBNA before exploration of the bronchial and excluding the cases that had a lesion on the tracheo bronchial tract at the point of puncture. In 1993, Utz et al. reported a sensitivity of 36% in 88 cases of bronchogenic carcinoma[10]. In 2004, Cetinkaya et al. reported a sensitivity of 100% in 15 cases of bronchogenic carcinoma and 65% in their 21 cases of tuberculosis[11]. The difference in the sensitivity of TBNA in our study and various other studies could be due to the multiple factors that influence the sensitivity of TBNA.

In our study, samples which provided a specific diagnosis were considered as True Positive (TP). This is in accordance with most of the studies, given the high positive predictive value (PPV) ascribed to TBNA[7,12,13,14]. All inadequate samples and those samples which failed to give a specific diagnosis in our study were considered as false negatives.

Adequate samples were obtained in 33 of the 42 i.e. 78.6% non small cell lung cancer patients. Among these patients, diagnosis could be established by TBNA for 25 patients (59.5 %). For the 17 patients who had negative TBNA, diagnosis was established for 11 patients by trans thoracic

needle aspiration. The remaining 6 patients with negative TBNA had malignant cells in their pleural fluid. All patients of non small cell lung cancer with negative TBNA were in advanced stages – 5 patients had metastasis to distant organs (stage 4), six patients had malignant pleural effusion (stage 4), 6 patients had great vessel and chest wall invasion with mediastinal lymphadenopathy but surgery could not be performed due to poor general condition. TBNA could be false negative due to either absence of metastasis to the lymph node or inadequate sample obtained on TBNA, but as surgery could not be performed on the above mentioned patients, all patients whose TBNA was negative were classified as false negative (FN).

In the small cell lung cancer group, adequate samples could be obtained for 5 of the 6 patients. Diagnosis was achieved by TBNA in 4 of these patients. The remaining 2 patients had malignant pleural effusion (Extensive Disease) and thus they were non candidates for surgery and were classified as False Negative (FN).

In the Tuberculosis group, adequate samples were obtained in 2 of the 4 patients of tuberculosis which suggested a granulomatous inflammation with necrosis. Ziehl Neelsen (ZN) staining in one of these patients was positive for Acid Fast Bacilli (AFB) and the other showed growth of Mycobacterium tuberculosis on Lowenstein Jensen Medium (LJ Medium). Both patients were given anti tubercular drugs and clinico radiologic follow up showed improvement in both these patients. Two patients had inconclusive TBNA cytology. Their diagnosis was eventually verified by sputum culture for Mycobacterium tuberculosis and clinico radiologic follow up which showed improvement with ATT. Thus, both the patients were classified as false negative.

In literature, there is substantial disagreement about the definitions of FN and TN, some studies had considered only adequate samples in the analysis which resulted in overestimation of the validity and reliability of TBNA[15,16]. In other studies, the definition of FN was based on the influence that the TBNA result had in the final decision about patient management[17].

In 15-25% of TBNAs, a representative sample is obtained but a specific diagnosis cannot be made because lymph node enlargement could also occur due to reactive lymph node hyperplasia without actual infiltration of the lymph node by tumour cells [18, 14].

Thus, in our study there is a possibility that the sensitivity of TBNA could have been under estimated as negative TBNA results could not be verified by a surgical gold standard.

Only 21-gauge cytology needles were used in our study for TBNA for diagnosis and simultaneous staging of bronchogenic carcinoma and their sensitivity evaluated. This could be a reason for lower sensitivity of TBNA in our study in comparison to some previous studies. Larger-caliber histology needles (18-gauge or 19-gauge) for TBNA have been reported to increase the yield over that of 21-gauge or 22-gauge needles in bronchogenic carcinoma

[19,20,21] and also have been shown to overcome the rare occurrence of false-positive cytologic results[20,22,23,9].

There was no statistically significant difference in outcome between benign and malignant disease in our study. Also, among the malignant diseases, no statistically significant difference was found between small cell lung carcinoma and non small cell lung carcinoma. In literature association has been found between the type of lesion and TBNA result[24,11,25,26,27,28]. Sharafkhaneh et al. in his study in 166 patients undergoing TBNA found that there were statistically significant correlations between TBNA result and cell type of the lesion, size of the lesion, and type of malignancy (small cell carcinoma more than non-small cell carcinoma more than lymphoma)[24]. This difference between our study and other reported studies could be due to the small number of small cell lung carcinoma and tuberculosis patients included in our study. However, according to a systematic review, these differences are not observed in most published studies when TBNA is performed with ultrasound (EBUS-TBNA) and the sensitivity of EBUS-TBNA is much higher than the reported in this study with conventional TBNA alone[29].

In our study, we did not find a statistically significant correlation between TBNA result and lymph node station punctured. This finding is in accordance with other studies which share similar results. Sharafkhaneh et al. [23]did not find any significant difference for aspiration yield between carinal and tracheal sites[24]. Similarly Fernandez-VillarA et al. did not find any statistically significant difference between TBNA results and the various lymph node stations punctured[30].

We found a statistically significant correlation between TBNA result and the size of lymph node punctured in our study. Similar findings have been previously reported by Harrow et al. who demonstrated that positive aspirates increased with a linear relationship from lymph nodes <1 cm to lymph nodes of 2–2.5 cm in size[12]. Similarly, Sharafkhaneh et al. and Fernandez-Villar A et al. found statistically significant correlation between lymph node size and TBNA result[24,30].

The most important limitation of our study is the lack of verification of the cases by a gold standard technique. This was because of the patients presenting to us in the advanced stages of the disease who were non candidates for surgery and their poor general condition. This problem has also been encountered in other reported studies[16]. Rapid on site evaluation by a cytopathologist has been shown to increase the sensitivity of TBNA in various studies [a, b]. This is another limitation of our study as ROSE was not done thus reducing the sensitivity of TBNA[31,32]. Another important limitation of our study is the low number of cases of small cell lung carcinoma and benign diseases in our study. Thus our study could be improved by enrolling a larger number of patients with benign diseases as well as malignant diseases.

In conclusion we would recommend TBNA for diagnosis of mediastinal lymphadenopathy in poor countries where

cost determines the usage of techniques as it can be a low cost and sensitive diagnostic method.

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