ORIGINAL

Yield Of Bronchoalveolar Lavage In Suspected Pulmonary TB With Negative Induced-Sputum Smear

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ABSTRACT

Background: Bronchoalveolar lavage (BAL) has been used to recover mycobacterium tuberculosis (MTB) from the respiratory tract of patients with lung infiltrates as nearly 50% of pulmonary tuberculosis (PTB) cases are sputum smear negative for acid fast bacilli (AFB). We prospectively compared the diagnostic yield of induced sputum (IS) smear with BAL smear and culture to assess its role in the early diagnosis of sputum negative PTB.

Methods: We performed bronchoscopy to obtain BAL in 52 consecutive patients of suspected PTB between December 2013 and November 2015 after negative results on 2 samples of IS smears. BAL samples were stained with Ziehl-Neelsen (ZN) stain and cultured on L-J media.

Results: Cohort of 52 IS negative patients had a mean age of 46 years (SD 15.6) with 58% male participants. Comorbidities were present in 31% participants whereas 42% were current smokers. Tuberculosis was the final diagnosis in 37% (n =19) patients and rest 63% (n = 33) had nontubercular etiologies like bronchiectasis (n = 6), pneumonia (n = 5), interstitial lung disease (n = 3), lung abscess (n = 2), lung cancer (n = 1), PCP (n = 1), hydatid cyst (n = 2), pneumonia (n = 5) and non-specific infection (n = 13). In tuberculosis group 33% patients had bronchoscopic abnormalities. Tuberculosis was confirmed by BAL-MTB culture in 90% (n = 17) and by biopsy in 10% (n = 2).

Conclusion: BAL has high diagnostic yield and should be considered in the evaluation of suspected PTB. Bronchoscopy also picked up alternative diagnoses. ***JMS 2016; 19(2):e1-e10***.

Keywords: Fiberoptic bronchoscopy (FOB), Bronchoalveolar lavage (BAL), Tuberculosis, Induced sputum

INTRODUCTION:

Worldwide tuberculosis (TB) particularly pulmonary tuberculosis (PTB) is a public health problem of immense proportions with main burden on developing countries which are resource limited. Detection of acid-fast bacilli (AFB) in respiratory specimens is recommended by World Health Organization (WHO) as the initial approach to the diagnosis of PTB[1] but in those patients who cannot produce sputum spontaneously this method has a low sensitivity.[2,3] Though relatively easy to perform sputum microscopy and culture can be negative in a significant proportion of PTB patients with sensitivities ranging from 25 to 45%.[4-6] Hypertonic saline induced sputum (IS) has been shown to increase the diagnostic yield of sputum examination. In the diagnosis of PTB both in terms of higher microscopy and higher culture positivity, results from various studies have confirmed the higher diagnostic yield of bronchoscopy over sputum examination. [10-12] In contrast some studies have shown no additional yield of bronchoscopy over IS.[13,14] Nearly 50% of PTB cases are sputum smear negative for AFB[15] and the transmission rate of smear negative TB has been reported as high as 22%.[16] Some studies suggest that close to 50% of sputum smear negative patients would ultimately need anti-tuberculosis therapy (ATT) if left untreated. [17,18] Therefore samples other than sputum have an important role in patients with occult tuberculosis or other conditions that mimic TB. Unanswered question is whether an invasive investigation like bronchoscopy is must or should we treat tuberculosis empirically on clinico-radiological grounds particularly in tuberculosis endemic countries. Empiric treatment may not only result in unnecessary cost and toxicity of ATT but we may also miss other mimicking diseases particularly malignancy. To address this dilemma we designed the present study to answer whether BAL obtained with bronchoscopy provides any additional diagnostic yield after at least two induced-sputum smear tests were reported negative in patients suspected of having active PTB.

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METHODS:

In the current study we prospectively evaluated 52 consecutive cases between December 2013 and November 2015, aged 20 years and above who had respiratory symptoms and radiographic findings suspicious of

PTB but were unable to produce sputum spontaneously and had at least two IS reports negative for AFB. Written informed consent was obtained from all eligible participants. Exclusion criteria included previous history of PTB, severe COPD, pregnancy and respiratory or cardiac failure. Detailed history, physical examination, complete blood count, coagulation profile, HIV serology and CT scan chest were done in all the patients included in the study. Patients suspected of PTB were first evaluated with induced-sputum smear specimen for AFB on at least two consecutive days. Morning induced sputum (IS) collection was performed by using 3% hypertonic saline nebulized through a mouthpiece using an ultrasonic nebulizer for at least 20 minutes. Samples were then centrifuged and concentrated and subjected to AFB smear examination.

Standard bronchoscopic premedication protocol published earlier by us was used [19] however we minimized the use of lidocaine as much as possible because of its known antimicrobial properties. [20] We obtained BAL specimens by wedging the bronchoscope into the radiologically most involved pulmonary segment and instilling four to six aliquots of 20 ml normal saline and aspirated until a total of 30 to 40 ml of fluid return was obtained. Using standard techniques all specimens were stained with Ziehl-Neelsen (ZN) stain for AFB and cultured in Löwenstein-Jensen (LJ) medium for the detection of mycobacterium tuberculosis (MTB). Definite PTB was defined as a positive culture for MTB in bronchoalveolar lavage fluid (BALF). All the participants were followed for at least 6 months after enrollment in the study.

RESULTS:

Cohort of 52 patients included in the present study had a mean age of 46 years (SD 15.6) with 58% male participants (Tables 1 and 2). Comorbidities mainly diabetes, chronic kidney and liver diseases were present in 31% of our patients whereas 42% participants were current smokers. Tuberculosis was the final diagnosis in 19 (37%) patients and rest 33 (63%) had nontubercular etiologies like bronchiectasis, community acquired pneumonia (CAP), interstitial lung disease (ILD), lung abscess, infected hydatid cyst or non-specific pulmonary infection (NSPI). There was no difference in the comparative age of the study subjects in relation to final diagnosis (Table 3). The main presenting symptoms cough, fever, hemoptysis and weight loss were not significantly different in tubercular and non-tubercular patients ($p > 0.8$). In tuberculosis group 33% patients had bronchoscopic abnormalities like endobronchial nodularity, mucosal irregularity and increased secretions in the radiographically involved lung. These patients had tuberculosis finally confirmed either by BAL-MTB culture 17 (90%) or by bronchial biopsy or transbronchial lung biopsy (10%) demonstrating caseating granulomas consistent with tuberculosis (Table 4). The two patients who had only biopsy evidence of PTB responded to six months anti-tuberculosis therapy with complete clinical and radiological improvement. All those patients who had BAL-AFB positive grew MTB on culture. In three patients a final diagnosis of ILD was made on the basis of TBLB and radiological findings. A 43 year chronic smoker was diagnosed to have small cell lung cancer from bronchial biopsy. This gentleman had fleeting infiltrates in serial radiographs and endobronchial growth in left upper lobe bronchus. Out of six bronchiectasis patients pseudomonas was isolated from BAL fluid of three. Two young males who had cavitation in upper lobes, hydatid membranes intrabronchially and positive hydatid serology had a final diagnosis of infected hydatid cysts. One 55 year old male smoker who had poorly controlled diabetes with diffuse ground glass opacity (GGO) on high resolution CT (HRCT) scan of chest had pneumocystis jirovici previously known as PCP in BAL fluid. Five patients were found to have community acquired pneumonia (CAP) and two lung abscess. We finally labeled 13 (25%) patients who did not fit into any known clinical entity as cases of nonspecific pulmonary infection (NSPI) because bronchoscopy and BAL fluid analysis could not reveal any specific etiology and there was complete clinical improvement on follow up with antibiotic therapy. No BAL specimen with a positive AFB smear or positive mycobacterial culture result was identified as MOTT or NTM. Both IS and BAL procedures were well tolerated by most patients and there were no major complication with either of the two procedures.

TABLE 1: Demographic features of the study population-Tuberculosis vs. Non-tuberculosis patients:

	TB group (n=19)		Non-TB group (n=33)		Total (n=52)		P value
Age ≥50 years	10	52.6%	14	42.4%	24	46.2%	0.477
Male gender	11	57.9%	19	57.6%	30	57.7%	0.982
Smoker	9	47.4%	13	39.4%	22	42.3%	0. 575
Co-morbidity	7	36.8%	9	27.3%	16	30.8%	0.7472
Presentation:							
Cough	10	52.6%	17	51.5%	27	51.9%	0.938
Fever	4	21.1%	8	24.2%	12	23.1%	0.793
Hemoptysis	4	21.1%	5	15.2%	9	17.3%	0.588
Weight loss	1	5.3%	3	9.1%	4	7.7%	0.618

TABLE 2: Demographic features of the study population-Tuberculosis vs. Non-tuberculosis patients:

Age (years)	N	Mean	SD	Range
Tuberculosis patients	19	47.00	14.57	21 - 74
Non-Tuberculosis patients	33	45.42	16.32	22 - 74
Total	52	46.00	15.58	21 - 74
P= 0.729				

TABLE 3: Comparative age of the study subjects in relation to final diagnosis:

Age (years)	Tuberculosis N = 19	ILD N = 3	Bronchiectasis N = 6	Lung Cancer N = 1	PCP N = 1	CAP N = 5	Hydatid cyst N = 2	Lung abscess N = 2	NSPI N = 13
Median	51.00	56.00	27.50			49.00	28.00	25.00	60.00
Mean	47.00	55.33	28.50	43	55	49.80	28.00	25.00	54.54
SD	14.57	4.04	6.09			13.92	4.24	2.83	15.22
Range	21 - 74	51 - 59	22 - 39			31 -70	25 - 31	23 - 27	28 - 74

CAP: community acquired pneumonia
ILD: interstitial lung disease
NSPI: nonspecific pulmonary infection

TABLE 4: Diagnostic methods used in the study population-Tuberculosis vs. Non-tuberculosis patients:

	TB group (n=19)		Non-TB group (n=33)		Total (n=52)		P value
Abnormalities on FOB	6	31.6%	9	27.3%	15	29.4%	0.650
BAL-AFB +ve	9	47.4%	0	0.0%	9	17.3%	<0.001
¥ BAL-MTB culture +ve	17	89.5%	0	0.0%	17	32.7%	<0.001
© Biopsy--TBLB / BB	6		5		11		-

- BAL: bronchoalveolar lavage, TBLB: transbronchial lung biopsy, BB: bronchial biopsy,
- MTB: mycobacterium tuberculosis
- ¥ [out of 19 TB patients 17 (90%) had MTB culture positive and remaining 2

(10%) had diagnosis based on biopsy].

- © [Biopsy was done only in those patients where it was judged to be important during bronchoscopy. In TB group, 4 patients had both culture and biopsy confirmation of TB whereas 2 had only biopsy confirmation of TB. In non-TB group, 3 biopsies revealed ILD, one small cell lung cancer and one biopsy was normal].

DISCUSSION:

Pulmonary tuberculosis (PTB) is a communicable disease with adverse public health consequences throughout the world. Nearly 50% of PTB cases are sputum smear negative for AFB [15] and the transmission rate of smear negative TB may be as high as 22%.[16] The investigation for sputum negative PTB differs between countries, depending upon economy and prevalence of TB. In countries with a high prevalence of TB and a high clinical suspicion, ATT is often initiated without further investigations. Ideally any patient with suspected PTB on clinical and radiological grounds requires further investigations to confirm the diagnosis. Moreover in view of the global challenge of spread and lethality of MDR and XDR-TB, it is important to stop the practice of empiric treatment in sputum negative cases of suspected PTB. The diagnostic yield of induced sputum is certainly more than that of spontaneously expectorated sputum however the unanswered question remains whether bronchoscopy provides any additional diagnostic yield over induced sputum. A study that compared the yield between spontaneous sputum, IS and bronchoscopy in patients with suspected PTB concluded that bronchoscopy had a significantly higher diagnostic yield than IS.[21] This study also reported that these investigations are complimentary to each other as the yield of any one modality was low and varied from 36% to 63%.Contrary to this two small studies in patients with negative IS did not find any additional yield by performing bronchoscopy.[13,22] The lower yield of bronchoscopy in these studies possibly may have resulted from the inexperience of the bronchoscopists and also from the use of lidocaine during bronchoscopy. Lidocaine is not only antibacterial and antifungal but it also has antimycobacterial properties and as little as 1 ml of 2% lidocaine in the tracheobronchial tree can reduce the culture positivity rate for M. tuberculosis by 50%.[23] In the present study we minimized the use of lidocaine and all bronchoscopic procedures were performed by one consultant.

In patients with sputum smear negative PTB, bronchoscopic interventions have been reported to enhance the diagnostic yield.[24-26] Both in terms of higher microscopy and higher culture positivity, results from various studies have confirmed the higher diagnostic yield of bronchoscopy over sputum examination.[10-12] In the present study we report the diagnostic yield of bronchoscopically obtained BAL fluid in 52 patients with suspected PTB and with at least two negative induced sputum (IS) specimens. Our results suggest that BAL is a useful and largely safe tool in the workup of sputum smear negative PTB.

The diagnosis of PTB in our study was confirmed in 37% of IS negative patients by BAL and biopsy. This included 90% by BAL-MTB culture and 10% by bronchial and transbronchial lung biopsies. Across the studies considerably different yields have been reported regarding the yield of bronchoscopy in the diagnosis of PTB[10,11,13,14,26-30] reflecting differences in study design and the patient population being studied. Some investigators proceeded directly to bronchoscopy without sputum induction and reported a high diagnostic yield between 32.5% [26] and 90%[10] for bronchoscopy. In sharp contrast to our 33% BAL- MTB culture positivity a study from Mayo Clinic, USA by Vivek[31] reported that bronchoscopy is useful in obtaining culture confirmation of PTB in only 10% of patients with negative results on multiple IS samples. This huge variation may possibly be due to very low prevalence of tuberculosis in that country. In the present study like an earlier report by Mohan [32] we have proven clearly the diagnostic utility of bronchoscopy in culture confirmation of TB after negative results on induced-sputum samples.

In countries like India where the prevalence of tuberculosis is high, patients having clinical and radiological picture compatible with TB but a negative sputum smear for AFB usually receive ATT at peripheral hospitals. One may argue in favor of this strategy as it is useful in most cases with the advantage of avoiding an invasive bronchoscopic procedure because smear-negative TB is a common problem in clinical practice. However, our study has exposed an important limitation of this strategy by diagnosing non-tubercular conditions particularly lung cancer and ILD for which ATT will not mean toxicity of unnecessary treatment but at the same time patient may be loosing the vital time by delayed diagnosis of actual disease. Therefore bronchoscopy and its related procedures such as BAL, bronchial and transbronchial lung biopsy is a safe pathway not only for the patient but also for the doctor whenever faced with such a diagnostic dilemma.

CONCLUSIONS:

Based on our results we conclude that, given its high diagnostic yield and safety, bronchoscopy and BAL should be considered in the evaluation of suspected induced sputum negative pulmonary tuberculosis. The usual practice of starting empiric anti-tubercular drugs in such patients should be discouraged because all that looks like TB on clinico-radiological grounds is not actually TB and bronchoscopy can pick up alternative diagnoses.

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