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Diagnostic value of bronchoalveolar lavage in the subset of patients with negative sputum/smear and mycobacterial culture and a suspicion of pulmonary tuberculosis

Mushtaq Ahmad[a], Wanis H. Ibrahim[b,*], Sabir Al Sarafandi[c], Khezar S. Shahzada[c], Shakeel Ahmed[c], Irfan Ul Haq[c], Tasleem Raza[d], Mansoor Ali Hameed[e], Merlin Thomas[c], Hisham Ab Ib Swehli[c], Hisham A. Sattar[c]

[a] Department of Medicine, Hamad General Hospital, Weill-Cornell Medical College, Doha, Qatar
[b] Hamad General Hospital, Qatar University and Weill-Cornell Medical College, Doha, Qatar
[c] Department of Medicine, Hamad General Hospital, Doha, Qatar
[d] Hamad General Hospital, Weill-Cornell Medical College, Doha, Qatar
[e] Hamad General Hospital, Doha, Qatar

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ABSTRACT

Background: The diagnostic value of bronchoalveolar lavage in patients with negative sputum/smear for tuberculous bacilli has been well studied. However, its value in the subset of patients with both negative sputum/smear and culture is seldom reported.
Methods: A retrospective study of patients referred for diagnostic bronchoscopy for the suspicion of pulmonary tuberculosis during the period from April 1st, 2015 to March 30th, 2016, and who had negative sputum/smear and culture for tuberculous bacilli.
Results: One hundred and ninety patients fulfilled the inclusion criteria. Bronchoalveolar lavage detected further 61/190 (32.1%) pulmonary tuberculosis cases. Bronchoalveolar lavage mycobacterial culture and polymerase chain reaction (positive in 60/190 (31.6%) and 58/190 (30.5%) of patients respectively) provided the highest diagnostic yield, whereas direct smear provided the lowest yield. Bronchoalveolar lavage had a sensitivity of 89.7%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 94.6%, and a test accuracy of 96.3% in suspected pulmonary tuberculosis cases with negative sputum/smear and culture. Positive bronchoalveolar lavage yield for tuberculosis was significantly associated with a positive QuantiFERON-TB Gold In-Tube test, positive purified protein derivative skin test, radiological evidence of upper zone abnormality and patient's origin being from the Indian subcontinent.
Conclusion: Bronchoalveolar lavage should be pursued as a useful diagnostic tool for suspected pulmonary tuberculosis cases when sputum/smear and culture are negative. Its value is higher in the subset of patients with positive QuantiFERON-TB Gold In-Tube test, positive purified protein derivative skin test, upper zone abnormality on radiograph or being from the Indian subcontinent.

Introduction

Tuberculosis (TB) is among the top 10 causes of death worldwide, and the leading cause from a single infectious agent. In 2017, TB caused an estimated 1.3 million deaths among Human Immunodeficiency Virus (HIV)-negative people, and an additional 300,000 deaths among HIV-positive people. About 10 million new cases of TB were diagnosed during the same year (World Health Organization, 2018). Infection with Mycobacterium tuberculosis (MTB) is acquired by inhalation of bacilli-containing droplet nuclei that are small enough (diameter 1–5 μm) to reach the alveoli (Long

* Corresponding author.
E-mail addresses: Mahmad5@hamad.qa (M. Ahmad), wanisian@yahoo.com (W.H. Ibrahim), sf.alsarafandi@gmail.com (S.A. Sarafandi), KSyed1@hamad.qa (K.S. Shahzada), SAhmed30@hamad.qa (S. Ahmed), IHaq@hamad.qa (I.U. Haq), tmohd1@hamad.qa (T. Raza), MHameed5@hamad.qa (M.A. Hameed), MThomas27@hamad.qa (M. Thomas), hswehli@hamad.qa (H.A.I. Swehli), HASATTAR@hamad.qa (H.A. Sattar).

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and Schwartzman, 2013). Pulmonary TB is the most common form of TB, accounting for about 85% and 70% of TB cases prior to and after the emergence of HIV respectively (Farer et al., 1979; Small et al., 1991). Early and prompt diagnosis of pulmonary TB is of paramount importance for the prevention of disease progression, spread to other contacts, and to avoid long-term sequelae. Direct sputum smear microscopy is the most widely used method for diagnosing pulmonary TB and is widely available in many countries. Recent studies have shown that a good-quality microscopy of two consecutive sputum specimens is able to identify the vast majority (95%–98%) of smear-positive TB patients (Davis et al., 2013; Ryu, 2015; World Health Organization, 2011). Consequently, the World Health Organization (WHO) recommends that only two sputum specimens are required and they may be performed on the same day, providing that acid-fast bacilli (AFB) microscopy is quality-assured. This can help to reduce the risk of defaulting during the diagnostic process, as well as the indirect costs of diagnosis to patients (World Health Organization, 2011). Nevertheless, despite being a rapid, simple, and inexpensive tool for diagnosing pulmonary TB, direct sputum microscopy has significant limitations. These limitations include the low and variable sensitivity (16–60%) and inability of some patients to produce sputum (Ryu, 2015; Harries, 2004). MTB culture is considered the gold-standard diagnostic test for TB. It has a higher sensitivity than AFB smear with the ability to detect 1×10^2 bacilli per ml. Furthermore, MTB culture has the advantages of distinguishing between non-tuberculous and tuberculous mycobacteria and ability to perform drug sensitivity testing. Nevertheless, the long time required for MTB culture and the significant laboratory infrastructure it requires are its major drawbacks (Harries, 2004; Cudahy and Shenoi, 2016). Previous studies have confirmed the ability of patients with sputum/smear-negative pulmonary TB to transmit the disease to other people. In fact, smear-negative patients with pulmonary TB contributed significantly to the incidence of the disease in different parts of the world (Behr et al., 1999). The threshold for detecting bacilli on light microscopy is about 5000–10,000 bacilli per ml, while the infecting dose of MTB is estimated to be fewer than ten organisms (Behr et al., 1999; Yeager et al., 1967; Hobby et al., 1973). TB remains a common health problem in the State of Qatar with an incidence of 40/100,000 population per year. About 97% of TB patients are expatriates (mostly from Asian countries with high TB prevalence). Qatar has a highly effective National TB Program with one National TB Reference Laboratory that performs a full range of laboratory diagnoses and a case detection rate exceeding 70%. All medications, laboratory and radiological investigations for diagnosis of TB are provided free-of-charge to all patients (Central Intelligence Agency, 2019; Khattab et al., 2015; AL-Suwaidi, 2015; Ibrahim et al., 2016). A number of previous studies have documented the diagnostic value of bronchoalveolar lavage (BAL) in patients with negative/sputum smear for AFB (Altaf Bachh et al., 2010; Quaiser et al., 2012). However, to the best of our knowledge, BAL value in patients with additional negative sputum/MTB culture has seldom been reported. The primary objective of this study was to evaluate the diagnostic yield of BAL in patients with suspected pulmonary TB (based on radiologic and/or clinical background) and in whom both sputum/direct AFB smear and MTB culture were negative. Secondary objective was to study the association between BAL TB yield in these patients and different patient and laboratory-related characteristics.

Methods

This was a retrospective study of adult patients who were referred to the Thoracic Center of Hamad General Hospital (HGH) for a diagnostic bronchoscopy based on radiologic and/or clinical suspicion of pulmonary TB during the period from April 1st, 2015 till March 30th, 2016. Patients who had at least two samples of sputum/AFB smear and MTB culture negative were included in the study. Patients with negative sputum/AFB smear but positive sputum/MTB culture, patients with positive sputum/AFB smear, patients with suspected extra-pulmonary TB and patients who were referred for bronchoscopy for reasons other than suspected pulmonary TB were all excluded from the study. Both electronic and non-electronic health records of the included patients were extensively reviewed by at least two investigators. Data regarding clinical and demographic characteristics, results of various laboratory and radiologic tests and the treating physician's final diagnosis (based on various tests and response to treatment) were recorded in a structured form.

Bronchoscopy and BAL technique at HGH

Bronchoscopy and BAL at HGH is performed according to the American Thoracic Society (ATS) guidelines (Meyer et al., 2012), using the Pentax flexible bronchoscope with minimal internal diameter of 2.0 mm. Sedation/anesthesia is achieved by intravenous Midazolam/Fentanyl with upper airway topical 10% Xylocaine spray. BAL is performed prior to other planned procedures and suction is avoided/minimized prior to BAL. Topical Lidocaine 2% is used to minimize cough but limited as much as possible to avoid its bacteriostatic effect. Bronchoscope is advanced till it is wedged in the desired sub-segmental bronchus based on radiological findings. Saline is infused in aliquots of 30 ml each followed by a gentle suction to collect the specimen in a collection trap. Total amount of saline used for infusion is 100– 300 ml with aim of return of 10–30% infused volume. Samples are submitted for MTB smear/culture and PCR and contain at least 10 ml volume of fluid.

Sputum collection and examination for suspected pulmonary TB at HGH

Sputum for AFB is collected at HGH according to the National Reference TB Laboratory, Hamad Medical Corporation (HMC) guidelines and the international standards (Hamad Medical Corporation, 2019; Lumb et al., 2019). Patients with suspected pulmonary TB are required to collect two first morning sputum samples on two separate days for AFB smear and MTB culture. Patients are requested to rinse the mouth with tap water, breathe deeply and cough several times to achieve a deep specimen (thick mucoid sputum and not saliva). Patient should expectorate into a dry, sterile and labeled container. The container is sealed tightly. Sputum induction procedure performed by a trained nurse (using hypertonic 3–5% saline nebulization) is used when a patient is not able to provide sputum samples. The National Reference TB Laboratory performs the following tests routinely on any sample of a suspected TB case: Fluorescence microscopy, Ziehl-Neelsen (ZN) staining technique, Polymerase Chain Reaction (PCR) (GeneXpert MTB/RIF assay) and MTB culture (both solid and liquid media using BACTEC MGIT 960 media).

Statistical analysis

Qualitative and quantitative data were expressed as frequency with percentage and mean ± SD with median and range. Descriptive statistics were used to summarize demographic and all other clinical characteristics of the participants. Associations between at least 2 qualitative or categorical variables were assessed using χ^2 test. For small cell frequencies, χ^2 test with a continuity correction factor or the Fisher exact test was applied. Pictorial presentations of the key results were made using appropriate statistical graphs. A 2-sided P value less than .05 was considered statistically

significant. Frequency and percentages were computed for calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using the standard formulae. Final treating physician's diagnosis that was based on results of different tests and response to treatment was considered as the gold standard. (All decisions to treat as TB in the State of Qatar are to be approved and monitored by the Communicable Disease Center – CDC after a thorough review of all test results). None of the primary treating physicians were involved in the study. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, Illinois).

Results

One hundred and ninety patients (all HIV-negative) fulfilled the study inclusion criteria. Mean age was 33 ± 10 years. Males constituted 85.3% of patients. Majority of patients were expatriates from the Indian subcontinent (77.4%), unskilled workers (85.6%) and asymptomatic (89.5%) (Table 1). Purified Protein Derivative (PPD) skin test was performed in 129 patients (positive in 92.2% "defined as induration of 10 mm or more") and QuantiFERON-TB Gold In-Tube test (QFT) in 54 patients (positive in 51.9%). All patients had abnormal chest radiographs with upper zone abnormality noted in 117/190 (61.6%). The most common abnormality on chest radiograph was pulmonary infiltrates (67.9%) (Table 2). BAL detected 61/190 (32.1%) pulmonary TB cases of the sputum/smear and culture-negative cases. Furthermore, BAL identified 2/190 (1.1%) malignancies, 4/190 (2.1%) fungal infections and 6/190 (3.2%) bacterial infections as the causes of abnormal chest radiographs. BAL/MTB culture and BAL/TB PCR (positive in 60/190 (31.6%) and 58/190 (30.5%) of patients respectively) provided the maximum diagnostic yield. BAL/direct AFB smear was positive in only 2/190 (1.1%) of cases. Using the final treating physician's diagnosis as the gold-standard, BAL had a sensitivity of 89.7%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 94.6%, and a test accuracy of 96.3% for the diagnosis of pulmonary TB in sputum/smear and culture-negative cases suspected of having the disease. Positive BAL yield was significantly associated with a positive QFT, positive PPD skin test, presence of upper zone abnormality on chest radiograph and patient's origin being from the Indian subcontinent (Tables 3 and 4).

Table 1
Characteristics of the study population.

Age (years) (n = 190)	
Mean	33.3 ± 10
Median	33
Gender (n = 190)	
Male	162 (85.3%)
Female	28 (14.7%)
Nationality (n = 190)	
Indian subcontinent	147 (77.4%)
Philippines	24 (12.6%)
Others	19 (10.0%)
Occupation (n = 187)	
Unskilled	160 (85.6%)
Semi-skilled	17 (9.1%)
Skilled	5 (2.7%)
Unemployed	5 (2.7%)
Smoking history (n = 190)	
Non-smokers	182 (95.8%)
Smokers	8 (4.2%)
Symptoms (n = 190)	
Asymptomatic	170 (89.5%)
Cough	11 (5.8%)
Fever	3 (1.6%)
Hemoptysis	6 (3.2%)

Table 2
Main laboratory and radiologic findings.

	N (%)
PPD skin test (n = 129)	
Positive	119 (92.2%)
Negative	10 (7.8%)
QFT (n = 54)	
Positive	28 (51.9%)
Negative	26 (48.1%)
Side of abnormality on chest radiograph (n = 169)	
Right side abnormality	86 (50.9%)
Left side abnormality	34 (20.1%)
Bilateral abnormality	49 (29.0%)
Lung zone involved on chest radiograph (n = 190)	
Upper zone	117 (61.6%)
Middle zone	11 (5.8%)
Lower zone	20 (10.5%)
More than one zone	42 (22.1%)
Main abnormality on chest radiograph (n = 168)	
Fibrosis	13 (7.7%)
Cavitation	23 (13.7%)
Infiltrates	114 (67.9%)
Mass	3 (1.8%)
Pleural thickening	1 (0.6%)
Pleural effusion	1 (0.6%)
Consolidation	9 (5.4%)
Miliary shadows	4 (2.4%)

Table 3
Yield and diagnostic utility of BAL.

Yield (n = 190)	
Negative yield	116 (61.1%)
Active pulmonary TB	61 (32.1%)
Malignancy	2 (1.1%)
Fungal infection	4 (2.1%)
Bacterial infection	6 (3.2%)
MOTT	1 (0.5%)
Positive BAL microbiologic tests (n = 190)	
Positive AFB smear	2 (1.1%)
Positive MTB complex PCR	58 (30.5%)
Positive MTB complex culture	60 (31.6%)
Diagnostic utility of BAL (n = 190)	
Sensitivity	89.7%
Specificity	100%
Positive predictive value	100%
Negative predictive value	94.6%
Accuracy	96.3%

Table 4
Association between BAL TB yield and different variables.

Variable		Positive BAL TB yield (N)	Negative BAL TB yield (N)	*P* value
Nationality	Indian subcontinent	43	104	0.045
	Philippines	13	11	
	Others	5	14	
Age (years)	20–40	49	93	0.356
	41–60	10	33	
	>60	2	3	
Occupation	Unskilled	56	104	0.211
	Semiskilled	2	15	
	Skilled	1	4	
	Unemployed	1	4	
PPD	Positive	48	71	0.011
	Negative	0	10	
QFT	Positive	9	19	0.026
	Negative	2	24	
Presence of respiratory symptom	Asymptomatic	57	113	0.220
	Respiratory symptoms present	4	16	
Abnormal side on chest radiograph	Right side	31	55	0.611
	Left side	10	24	
	Bilateral	14	35	
Abnormal zone on chest radiograph	Upper Zone	45	72	0.019
	Mid Zone	2	9	
	Lower Zone	1	19	
	More than one zone	13	29	
Main abnormality on chest radiograph	Fibrosis	5	8	0.261
	Cavitation	11	12	
	Infiltrates	38	76	
	Mass	0	3	
	Pleural thickening	0	1	
	Pleural effusion	0	1	
	Consolidation	1	8	
	Miliary seeds	0	4	

Discussion

Subjects with untreated TB can infect up to 10 people over a year. Sputum/smear-negative TB is a common clinical problem and constitutes a diagnostic challenge to physicians. Besides being able to infect other people, delayed diagnosis of smear-negative pulmonary TB is a cause of significant mortality and morbidity and can lead to irreversible lung damage (Lumb et al., 2019). Hence, the Stop-TB-Strategy emphasizes the timely diagnosis and treatment of all cases of TB, including smear-negative pulmonary TB (Shah et al., 2012; WHO, 2007). Sputum/culture-negative TB is another entity of pulmonary TB that is encountered in developed and developing countries. In New York City, approximately 27% of TB cases are reported to be culture-negative (Annual TB summary, 2013). In 2013, the Center for Disease Control (CDC) has reported a 23% culture-negative rate for TB cases in the United States (Centers for Disease Control and Prevention, 2013–2015; Asghar et al., 2018). Fiberoptic bronchoscopy is a relatively safe procedure. Since its introduction in the 1960s, published rates of complication from fiberoptic bronchoscopy have ranged from <0.1 to 11%, with mortality generally reported between 0 and 0.1% (Stahl et al., 2015). Among the many advantages of fiberoptic bronchoscopy in TB diagnosis are visualizing endobronchial abnormalities and feasibility for BAL, biopsy, and tissue sampling. The current study confirmed the important value of BAL via fiberoptic bronchoscopy in subjects with both sputum smear and MTB culture-negative subjects with clinical suspicion of pulmonary TB. BAL could identify 61/190 (32.1%) of those patients as pulmonary TB cases. This finding is in agreement with findings from previous studies that investigated the value of BAL/washings in sputum smear-negative pulmonary TB cases. In 1982, Soe et al. performed a fiberoptic bronchoscopy on 65 patients suspected of having active pulmonary TB who were either sputum/smear-negative or had no sputum to test. They reported a positive diagnostic yield of 38% in bronchial aspirate (So et al., 1982). Altaf Bachh et al. in a prospective study of 75 suspected sputum/smear-negative pulmonary TB cases found bronchial washings were the only diagnostic method in 48.33% of cases (Altaf Bachh et al., 2010). In a recent cross-sectional study, Krishnan et al. reported a diagnostic yield of bronchial washings/AFB smear of 26.9% and culture of 44.23% (Navaneedha Krishnan and Allwyn Vijay, 2017). Higher yield of up to 86.6% was reported only occasionally (Kalawat et al., 2010). A striking finding in the current study is the very low yield of BAL/AFB smear in subjects with negative sputum/AFB smear and MTB culture. To the best of our knowledge, this finding was seldom reported in the literature. Previous studies that demonstrated a significant yield of BAL/AFB smear included mainly sputum/smear-negative but not sputum culture negative cases. Our finding may question the role of BAL/AFB smear in the subset of patients who demonstrated a negative sputum/MTB culture. The yield of BAL in the current study was mainly derived from the MTB culture and TB PCR, which emphasizes the importance of performing these tests on BAL specimens when suspecting pulmonary TB in patients with negative sputum/AFB smear and MTB culture. Such diagnostic value of TB PCR and MTB culture in sputum/smear-negative patients with clinical suspicion of pulmonary TB have also been reported by other investigators (Tamura et al., 2010). The current study has also demonstrated a higher diagnostic utility (in terms of sensitivity, specificity, PPV and NPV) of BAL in patients with negative sputum/AFB smear and MTB culture compared to the few previous studies that addressed such values. Nikbakhsh et al. reported BAL sensitivity, specificity, PPV and NPV of 60%, 91%, 89% and 64% respectively (Nikbakhsh et al., 2015). Nevertheless, the very high PPV observed in the current study could be influenced by the prevalence of TB in the included subjects. In the current study, we have shown that as many as 96% of subjects whose BAL tests were negative for TB did not actually have active pulmonary TB. An important finding in our study is the

significant association between BAL TB yield and a positive QFT, a positive PPD skin test, presence of upper zone abnormality on chest radiograph and patient's origin being from the Indian subcontinent. This finding emphasizes the importance of a vigilant search for TB in patients with these clinical characteristics despite being sputum/smear and culture-negative. Our study is among the first to confirm the diagnostic value of BAL in the subset of patients with both sputum/ AFB smear and MTB culture-negative pulmonary TB. Furthermore, the relatively large number in the study population adds more weight to the results. Besides the significant yield of BAL in patients with sputum/AFB smear and MTB culture-negative cases, we have also documented significant associations between the positive BAL TB yield and different patients' clinical and laboratory characteristics as well as studied the diagnostic utility of BAL in terms of sensitivity, specificity, negative and positive predictive values. Such results were seldom reported in previous studies (Nikbakhsh et al., 2015). Besides the limitations inherent to retrospective studies, an important limitation of the current study was the use of final treating physician's diagnosis as the gold standard to determine the sensitivity, specificity, PPV and NPV of BAL. Nevertheless, based on an extensive review of the medical records of patients included in this study, the physician's final diagnosis was based most of the time on objective parameters such as other diagnostic tests or appropriate response to particular therapies. Furthermore, the current study has included only subjects referred for bronchoscopy for suspicion of pulmonary TB. Subjects who were referred for reasons other than suspicion of pulmonary TB were excluded. A selection bias, is therefore, could have been created. A number of previous studies have documented the role of post-bronchoscopy sputum collection in diagnosing pulmonary TB in sputum/smear negative cases suspected of having the disease (George et al., 2011). Unfortunately, post-bronchoscopy sputum is not routinely collected for suspected TB cases in our institution. Furthermore, the current study did not examine drug sensitivity of the MTB detected in BAL specimens.

Conclusion

The current study suggests that BAL is a useful tool in diagnosing pulmonary TB in the subset of patients with negative sputum/AFB smear and MTB culture who are suspected of having the disease. Positive BAL yield in this subset of patients is significantly associated with a positive QFT, a positive PPD skin test, presence of upper zone abnormality on chest radiograph and patient's origin being from the Indian subcontinent. Patients with these clinical features should be a particular target of BAL evaluation when sputum studies prove to be negative.

Conflict of interest

None of the authors has any conflict of interest to declare.

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None.

Ethical approval

The study was approved by the Institutional Review Board of Hamad Medical Corporation (Doha, Qatar) (IRB No. 16224/16).

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