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Role of Fiberoptic Bronchoscopy in the Rapid Diagnosis of Sputum Smear-negative Disseminated Tuberculosis with Pulmonary Miliary Infiltrates

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ABSTRACT

Objectives: We sought to evaluate the role of bronchoscopy-related procedures such as bronchoalveolar lavage (BAL), bronchial wash (BW), bronchial brush (B brush), transbronchial biopsy (TBB), and post-bronchoscopy sputum (PBS), alone or in combination, in the rapid diagnosis of negative sputum smear disseminated tuberculosis (TB). ***Methods***: We performed a secondary post hoc analysis of data collected from our previous study entitled "Disseminated tuberculosis among adult patients admitted to Hamad General Hospital, Qatar: A five-year hospital-based study" with a modified objective. ***Results:*** We identified 27 patients. BAL fluid was positive for acid-fast bacilli (AFB) smear in 7/27 (25.9%) patients and were culture-positive for *Myobacterium tuberculosis* in 17/27 (63.0%) cases, while BW collections were smear-positive in 9/27 (33.3%) cases and culture-positive for *M. tuberculosis* in 18/27 (66.7%) cases. TBB showed caseating granulomas in 10/16 (62.5%) cases and one case of non-caseating granuloma (6.3%). PBS was positive for AFB in 4/8 (50.0%) patients. The combination of these procedures enabled us to diagnose disseminated TB rapidly in 22 (81.5%) cases. ***Conclusions:*** Bronchoscopy proved to be an effective method for the rapid diagnosis of disseminated TB in patients in whom sputum smear microscopy was negative.

Tuberculosis (TB) is one of the world's top 10 causes of death. It affects millions of people every year.[1,2] In 2017, TB caused approximately 1.3 million deaths among HIV-negative people with an additional 300 000 deaths from TB among HIV-positive people.[1] Disseminated TB is a potentially fatal form of TB if untreated.[3] It is defined as a mycobacterial disease that has two or more non-contiguous sites resulting from hematogenous dissemination of *Mycobacterium tuberculosis*. It may occur due to progressive primary infection, reactivation of a latent focus with subsequent spread, or rarely through iatrogenic origin.[4]

The exact global incidence of disseminated TB is not yet clear; however, among immunocompetent adults, it is estimated to account for < 2% of all TB cases and up to 20% of all cases of extrapulmonary TB.[5] In Qatar, disseminated TB accounts for 2.6% of all extrapulmonary tuberculosis,[4] while in Oman it is estimated to account for 10% of all TB cases.[6] As a result of hematogenous spread, disseminated TB can affect multiple organs leading to protean and nonspecific clinical manifestations. The lung is the most commonly affected organ, and patients usually present with miliary infiltrates on chest radiography. Sputum examination is usually unhelpful, and the diagnosis is usually delayed or mistaken owing to the low incidence of positive acid-fast bacilli (AFB) staining.[4] Sputum culture may increase the diagnostic yield, but it is usually obtained late, and some clinicians initiate early empirical treatment of possible disseminated TB based on the miliary pattern on chest radiography, which is often incorrect and cannot replace or support etiological confirmation.

Therefore, physicians must resort to other techniques, such as fiberoptic bronchoscopy, to support the early diagnosis of disseminated TB and rule out other pathological processes.

Fiberoptic bronchoscopy is used successfully in the early diagnosis of pulmonary TB by microbiological studies including bronchoalveolar

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lavage (BAL), bronchial wash (BW), bronchial brush (B brush), and histological examination of transbronchial biopsy (TBB).[7,8] However, there are few reports of the role of fiberoptic bronchoscopy in the rapid diagnosis of smear-negative disseminated TB in patients with pulmonary miliary infiltrates.[9–11]

The objective of this study was to evaluate the role of bronchoscopy-related procedures such as BAL, BW, B brush, TBB, and post-bronchoscopy sputum (PBS), alone or in combination, in the rapid diagnosis of negative sputum smear disseminated TB in patients with pulmonary miliary infiltrates.

METHODS

We performed a secondary post hoc analysis of collected data from our previous study entitled "Disseminated tuberculosis among adult patients admitted to Hamad General Hospital, Qatar: A five-year hospital-based study"[4] with a modified objective, which was the role of fiberoptic bronchoscopy in the rapid diagnosis of sputum smear-negative disseminated TB. The outcome was also modified to be the total number of patients who were diagnosed rapidly with the help of bronchoscopy. The primary study was a retrospective observational study that was conducted at Hamad General Hospital, Qatar, which is a tertiary center that covers all specialties except for cardiology, hematology-oncology, and obstetrics. It involved all patients 15 years of age or older who were admitted to Hamad General Hospital with disseminated TB, from 1 January 2006 to 31 December 2010.

From the primary study, we selected cases that had miliary infiltrate on chest radiography and underwent bronchoscopy due to a sputum negative AFB smear. We described the demographic and clinical characteristics of these patients as well as the role of fiberoptic bronchoscopy in the rapid diagnosis of suspected disseminated TB in these patients.

Diagnosis of disseminated TB was considered as rapid and early if there was a radiographic finding of miliary lung lesions plus one of the following:

1. Samples of BAL, BW, B brush, or TBB were smear-positive for AFB.
2. A PBS sample was smear-positive for AFB or,
3. TBB sample showed caseating granulomas on histology test or was smear-positive for AFB.

After bronchoscopy, BAL, B brush, and BW specimens were assessed for AFB microscopy by Ziehl-Neelsen technique and culture for *M. tuberculosis* on conventional Lowenstein-Jensen and Bactec MGIT 960 liquid medium.

Since this was a secondary post hoc analysis of collected data from our previous study, no ethics committee approval or informed consent was required as the original study was approved by the Medical Research Ethical Committee at Hamad Medical Corporation, Qatar.

Data analysis was performed with SPSS (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). The results of analyses of continuous variables are expressed as means and standard deviations (SD) unless otherwise specified.

RESULTS

A total of 27 patients were included in this posthoc analysis. There were 24 (88.9%) males and three (11.1%) females. The mean±SD age of the patients was 32.2±13.6 (range: 15–67 years). Fever was the most common symptom (100%), followed by anorexia (77.8%). Non-Qatari patients predominated (92.6%), and all patients were HIV-negative. Table 1 summarizes the demographic and clinical aspects of the 27 patients involved in this study.

Before bronchoscopy, the sputum samples for AFB were all negative. Sputum cultures were positive for *M. tuberculosis* in 18/27 (66.7%) cases after four to six weeks.

Bronchoscopy was performed in the 27 patients a few days after the negative sputum smear. BAL fluids were AFB positive in 7/27 (25.9%) cases and culture-positive for *M. tuberculosis* in 17/27 (63.0%) cases, while BW collections were AFB positive in 9/27 (33.3%) cases and culture-positive in 18/27 (66.7%) cases. B brush was done in two cases; none of them showed AFB or grew mycobacteria on culture.

TBBs were obtained in 16 patients. Granulomas were found in 11/16 (68.8%) cases. Caseating granulomas were obtained in 10/16 (62.5%) cases and one case of non-caseating granuloma (6.3%). Five biopsies were subjected to smear AFB and mycobacterial culture at the same time with 3/5 (60.0%) of cases were smear AFB and culture-positive. The case of non-caseating granuloma revealed positive AFB in BAL and BW samples.

Post-bronchoscopy sputum was sent for eight (29.6%) patients; four (50.0%) were AFB positive,

Table 1: Demographic and clinical characteristics of the 27 patients involved in this study.

Variables	n (%)
Sex	
Male	24 (88.9)
Female	3 (11.1)
Age, mean ± SD (range years)	32.2 ± 13.6 (15–68)
Nationality	
Qatari	2 (7.4)
Non-Qatari	25 (92.6)
Clinical picture	
Fever	27 (100)
Anorexia	21 (77.8)
Cough	19 (70.4)
Weight loss	19 (70.4)
Night sweat	13 (48.1)
Weakness	13 (48.1)
Headache	8 (29.6)
Vomiting	4 (14.8)
Diarrhea	4 (14.8)
Splenomegaly	9 (33.3)
Hepatomegaly	7 (25.9)
History of contact with sick persons	5 (18.5)
Underlying conditions	
Diabetes mellitus	3 (11.1)
Alcoholics	1 (3.7)
Hypertension	1 (3.7)
End-stage renal disease	1 (3.7)
Positive PPD	13 (48.1)

SD: standard deviation; PPD: purified protein derivative.

and all were culture-positive for *M. tuberculosis*. Table 2 describes the histopathological and microbiological results for different biopsies obtained by fiberoptic bronchoscopy from disseminated TB patients involved in this study. Therefore, a rapid diagnosis of disseminated TB was established in 22 (81.5%) cases.

DISCUSSION

Patients with smear-negative sputum and miliary infiltrate on chest radiography are challenge for clinicians, since these findings are not specific to disseminated TB and can be mimicked by other conditions such as histoplasmosis, sarcoidosis, pneumoconiosis, metastasis, bronchoalveolar carcinoma, and pulmonary siderosis.[10,12] Microbiological proof of TB is critical not only to confirm the diagnosis but also to elucidate the drug sensitivity of the organism. However, waiting for culture results will delay the treatment whereas the initiation of antituberculous treatment empirically based on the miliary pattern alone may mask or delay the diagnosis of other pathologies. Therefore, other diagnostic modalities, such as fiberoptic bronchoscopy, are required.

Fiberoptic bronchoscopy has been widely used as an alternative diagnostic modality for early diagnosis of smear-negative pulmonary TB in patients with non-miliary infiltrates on chest X-ray. However, few reports have addressed the role of bronchoscopy in the rapid and early diagnosis of disseminated TB in patients with miliary infiltrate on chest radiography.[9–11] Fiberoptic bronchoscopy and related procedures such as BAL, BW, and TBB are essential to obtain suitable samples, which must be subjected to smear AFB, polymerase chain reaction (PCR), and culture methods for isolation of *M. tuberculosis*, while biopsy should be additionally subjected to histopathology examination to detect caseating granulomas. The results of the bronchial aspirate smears are usually obtained within one week, allowing for rapid diagnosis of TB before the availability of confirmatory bronchial aspirate cultures for *M. tuberculosis*. Nucleic acid amplification (NAA) tests using PCR in bronchial aspirate specimens have recently been used as a rapid diagnostic tool for

Table 2: Histopathological and microbiological results for different biopsies obtained by fiberoptic bronchoscopy from disseminated tuberculosis patients involved in this study.

Samples	Caseating granuloma, n (%)	Non-caseating granuloma, n (%)	AFB positive, n (%)	Culture-positive, n (%)
Transbronchial biopsy	10 (62.5)	1 (6.3)	3 (60.0)	3 (60.0)
Bronchoalveolar lavage	NA	NA	7 (25.9)	17 (63.0)
Bronchial wash	NA	NA	9 (33.3)	18 (66.7)
Bronchial brush	NA	NA	0/2	0/2
Post-bronchoscopy sputum	NA	NA	4 (50.0)	8 (100)

Data given as n (%).
NA: not applicable.

TB. GeneXpert MTB/RIF assay is an example of NAA test, which simultaneously detects DNA of *M. tuberculosis* complex and resistance to rifampin (RIF) in less than two hours.[13] Unfortunately, this test was not available in our laboratory during the study period.

In our study, BAL and BW were useful ancillary procedures in the rapid diagnosis of the disease. BAL smears achieved a yield of seven (25.9%) positive samples for AFB, which falls within the range of 5% and 47% achieved by previous studies.[11,14–16] BW smear was positive in 33.3% of our cases, which exceeds the diagnostic yield reported in previous studies (which ranged between 0 and 7%).[10,17,18] On the other hand, B brush fluid had no contribution in our study since neither of the two samples showed AFB, whereas, in previous studies, positive B brush smear varied from 0% to 31% of cases.[9,11] Despite the wide range of differences in the results, which can be attributed to the experience of the bronchoscopist, differences in the procedural techniques, patient cooperation, the amount of fluid used for irrigation and the dose of xylocaine used, it is obvious that these procedures have a significant contribution in the rapid diagnosis of disseminated TB.

In our study, histology of TBB showed caseating granulomas in 10/16 (62.5%) patients and was the only diagnostic feature in these patients. This was comparable to the study done by Aggarwal et al.[10] (67.7%), but less than the study conducted by Lopez et al.[11] (88%) and higher than that done by Willcox et al.[9] (57%).

In four (50.0%) out of eight patients, the PBS sample showed the presence of AFB, providing additional evidence for rapid diagnosis of disseminated TB in four patients. These findings have two implications in practice. Firstly, it showed the significance of sending PBS samples for AFB smear and culture to increase the diagnostic yield. Secondly, it has important implications for the control of infections, since it showed the conversion of a significant number of cases to more infectious after bronchoscopy.

As noted in this study, a combination of positive AFB smear and histology results of bronchoscopy-related procedures enabled us to diagnose disseminated TB rapidly in 18 (66.7%) patients, which was similar to previous studies.[10,11] Moreover, the use of PBS for AFB as a diagnostic method, allowed us to obtain the diagnosis in four out of eight patients, increasing the total number significantly to 22 (81.5%).

Some limitations were observed in this study. First, its retrospective nature, and second, we could not perform PCR since it was not available in our laboratory during the study period. Third, the relatively small sample size, in addition to being hospital-based means that the results may not apply to other hospitals.

Despite these limitations, we believe that our study is one of the few reports that reaffirms the value of bronchoscopy in the rapid diagnosis of sputum smear-negative disseminated TB in patients with miliary shadowing on chest radiography and has an additive value to the literature.

CONCLUSION

Bronchoscopy proved to be an effective method for the accurate and rapid diagnosis of disseminated TB in patients in whom sputum smear microscopy was negative. The combination of TBB, BAL, BW, as well as PBS collection, increases the overall rapid diagnostic yield.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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