

Original Research Article

Value of bronchoscopy in the diagnosis of sputum smear negative pulmonary tuberculosis

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Received: 14 June 2017

Accepted: 08 July 2017

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ABSTRACT

Background: Bronchoscopy has been found to be applicable in diagnosing suspects of pulmonary TB which have no sputum or sputum smear negative for acid fast bacilli. Additionally, it is helpful in the diagnosis of endobronchial tuberculosis, allowing early detection of broncho stenosis.

Methods: A prospective study, where bronchoscopy was conducted in 167 patients with acid-fast bacillus sputum smear negative. The average age of the patients was 44.1±19.4, from age 15 to 87 years old, higher frequency in age from 20-40 years old and 55-64 years old.

Results: From 167 patients in the study, endoscopic presentation resulted: normal in 7 (4.2%) cases, bronchitis - 60 (35.9%) cases, oedematous-hyperaemic - 62 (37.1%) cases, caseous inflammation - 7 (4.2%) cases, ulcerative lesions - 3 (1.8%) cases, tumoral lesions - 21 (12.6%) cases and fibrous stenotic changes in 7 (4.2%) patients. From 44 (26.3%) patients to whom was obtained biopsy, the histological examination has resulted: 24 (54.5%) cases with TB granuloma, 14 (31.8%) - epithelioid granulomas and in 6 (13.6%) cases resulted non-specific inflammation. The examination of bronchial washing for acid-fast bacillus smear concluded the diagnosis in 40.4% of cases, the examination for acid-fast bacillus smear collected after diagnostic FBS has been decisive in 53.9% of cases. The examination for acid-fast bacillus culture resulted positive in 70.5% of bronchial washing and in 61.2% of sputum collected after FBS.

Conclusions: Fiberoptic bronchoscopy plays the key role to the patients with suspected tuberculosis which are acid-fast bacillus smear negative or that have no sputum.

Keywords: Bronchoscopy, Bronchial washing, Endobronchial Tb lesions, *Mycobacterium tuberculosis*, Pulmonary tuberculosis

INTRODUCTION

Bronchoscopy provides extensive information on all lung pathologies. This examination takes on importance in lung tuberculosis to point out the degree of bronchial damage from the tuberculosis process. It is especially necessary for differential diagnosis, when discussing the presence of bronchopulmonary neof ormation or other

serious illnesses. In addition, it is necessary to obtain bacteriological examination material for *Mycobacterium tuberculosis* and other germs by the bronchial washing as well as for histopathological examinations.¹⁻¹¹ Lungs with TB, which it depends on the degree of damage to the bronchial tree, might be observed: hyperemia of the bronchial mucous membranes, various bronchial secretions, such as hematic, serous, etc. The appearance

of Aden bronchial fistula is a valid fibro-bronchoscopic sign of tuberculosis. Furthermore, the bronchoscopy provides biopsy of bronchial mucous membrane, tracheobronchial and pulmonary ago biopsies, bronchial washing for *Mycobacterium tuberculosis*, bronchial brushing, and so on.^{1,3,6-12} Pulmonary TB is nowadays shifted to older ages, which is also affected by pulmonary cancer, making differential diagnosis difficult. In these cases, FBS, with its macroscopic findings and mainly with the different bronchoscopic specimens including biopsy, brushing and washings, helps greatly in determining the exact diagnosis of bronchial TB.

FBS examination is useful in the suspected cases of pulmonary TB, and especially those with atypical clinical presentation or when the diagnosis is not achieved with bacteriological confirmation. During the endoscopic examination, the bronchial changes, which are divided into two main groups, in the non-specific and specific bronchial lesions are noticed.

Bronchial washing for bacteriological examination increases the value of bronchoscopy to obtain the most accurate diagnostic results. Macroscopic and histopathological presentation complements the framework of tuberculosis pathology and often makes differential diagnosis with other pathologies, especially with bronchial carcinoma.

Microscopic microbial detection is a credible criterion of infectivity. Sensitivity is 22-78%, the specificity is different- depending on the prevalence of nontuberculous mycobacterial infection - the predictive positive value > 90%.¹³ Excluding the possibility of tuberculosis is a common clinical situation. The older patients, the chronic lung disease, and the increased use of immunosuppressants increase the risk of tuberculosis reactivation and have created an increasingly common scenario where infective active tuberculosis should be quickly excluded and with minimal difficulty.

Tuberculosis is also often a “great mimic”. TB can present similar clinical features to many chronic lung diseases from pneumonia to emphysema. Exclusion of TB simply based on anamnesis, clinical examination or radiography is very difficult. It is also necessary to exclude tuberculosis with more safety than other diseases due to public health issues of tuberculosis infection. Although for TB diagnosis, there are many opportunities, including new diagnostic methods, there are still made mistakes in the diagnosis of tuberculosis, due to various causes.¹⁴ Decreasing the tuberculosis incidence is associated with increasing of diagnostic errors for the diagnosis of this disease. False positive and false negative diagnosis have a considerable influence on prognosis.

The study aims to evaluate the diagnostic performance of fiberoptic bronchoscopy in patients who are suspected of having tuberculosis, are acid-fast bacillus smear negative or cannot produce sputum.

METHODS

The paper is a prospective and observational cohort study. A total of 167 adolescent patients were hospitalized at the university hospital “Shefqet Ndroqi” from January 1, 2011 until December 31, 2015 with different diagnoses of pulmonary pathology or who were suspected of having sputum smear negative pulmonary TB, whose final diagnosis has been pulmonary TB (Table 1). In all patients, fiberoptic bronchoscopic examination was performed, followed by bronchial washing for *M. tuberculosis* smear and culture examination. The bronchial washing was performed in areas with pathological changes, if these were present. In patients with endobronchial abnormalities, it was performed a biopsy and histopathological examination, and the material was examined for *M. tuberculosis* smear and culture.

Table 1: Characteristics of patients in the study.

Variables	Mean±SD	Min.- max
Age (years)	44.10±19.14	15.00-87.00
PPD	20.22±4.82	12.00-30.00
Diagnosis period (days)	7.01±4.18	2.00 -40.00
Time from start of complaints	65.59±57.94	2.00-300.00
Period of hospitalization	18.86±10.55	1.00-90.00
After how many days is performed FBS	4.58±2.88	1.00-23.00

The endoscopy was performed with flexible Olympus BF IT 180-6.0 mm video bronchoscope. Before the procedure, patients were anesthetized with local lidocaine anesthesia 2%-20 ml and 3-5 mg midazolam i/v. Samples were examined for *M. tuberculosis* smear and culture. The bioptic material is stored in sol. formalin and it is histopathologically examined and with special staining technique for *Mycobacterium*.

The criteria for the diagnosis of pulmonary tuberculosis are according to the national TB program standards, including positive smear and culture for *M. tuberculosis*, caseous necrosis granuloma, supporting the diagnosis are considered epithelial granulomas and positive response to the application of treatment regimens.

Inclusion criteria

- Age at least 18 years
- Sputum smear negative for *M. tuberculosis* in 2 or more specimens or without sputum production
- FBS were performed due to diagnostic suspicion before beginning anti-TB treatment.

Exclusion criteria

- Patients having any contraindications for flexible fiberoptic bronchoscopy

- Positive sputum smear for *M. tuberculosis*
- Patients not giving consent for fiberoptic bronchoscopy
- Patients with unconfirmed diagnosis due to loss of observation.

RESULTS

Fibro bronchoscopy was performed in 167 patients with Acid-fast bacillus smear negative. The mean age of the patients was 44.1±19.4, from 15 to 87 years old, with a higher frequency in age between 20-40 years and 55-64 years. There were predominantly male (65.3%), women (34.7%), which coincides with the frequency of tuberculosis in the ratio M/F = 2/1 (Figure 1).

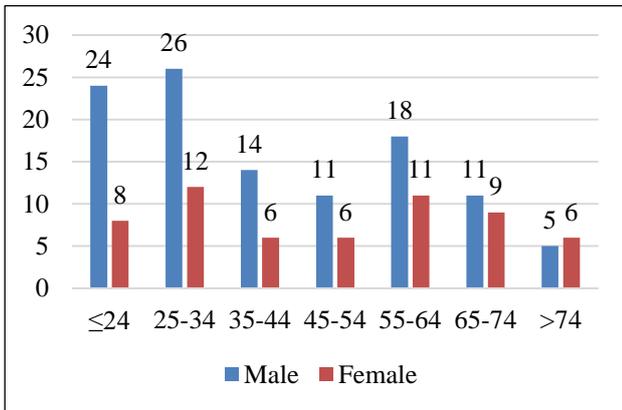


Figure 1: Patients according to the gender and age.

The diagnosis of hospitalization (Figure 2) in 76 (45.5%) patients was pulmonary tuberculosis. In other patients, the diagnosis was wrong - in 49 (29.3%) for pneumonia, 13 (7.8%) for pulmonary malignancy, 7 (4.2%) for pulmonary fibrosis, 2 (1.2%) for COPD, 2 (1.2 %) for bronchial asthma, 2 (1.2%) for pulmonary effusion and in 16 (9.6%) patients for other pathologies. In 3 (1.8%) patients, there were personal anamnesis for TB and in most cases the tuberculin skin test was positive.

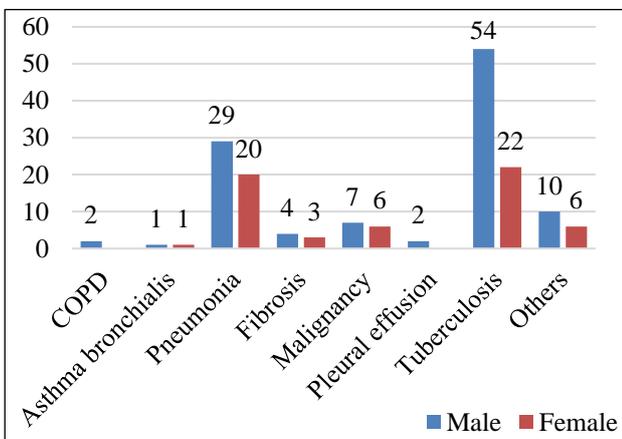


Figure 2: Patients according to the gender and diagnosis on admission.

The fiber bronchoscopy with bronchial washing and other examinations for pulmonary TB was performed on average 4.58±2.88 (from 1 to 23 days) days after hospitalization, often in 2-5 days after hospitalization - in 130 (77.8%) patients.

There were diagnosed 39 (23.4%) patients with concomitant diseases. Out of these concomitant diseases, the most frequent one resulted Diabetes mellitus, followed by cardiovascular diseases, COPD and psychic disease.

From 167 patients in the study, it resulted 154 (92.2%) patients with infiltrative TB, out of whom 21 (12.6%) were in the destructive phase; 4 (2.4%) patients had the diagnosis of miliary TB and 8 (4.8%) - TB hilar adenopathy (Figure 3). In relation to diagnosis, if it was noticed in proportion to the number of cases by gender, it was shown that the frequency of infiltrative forms (plus destructive phase) was approximately the same as for men and women respectively 92% and 91.3%, the miliary TB was often in women respectively 1.8% and 3.4% and less frequent with TB hilar adenopathy, respectively, 5.17% and 4.6%.

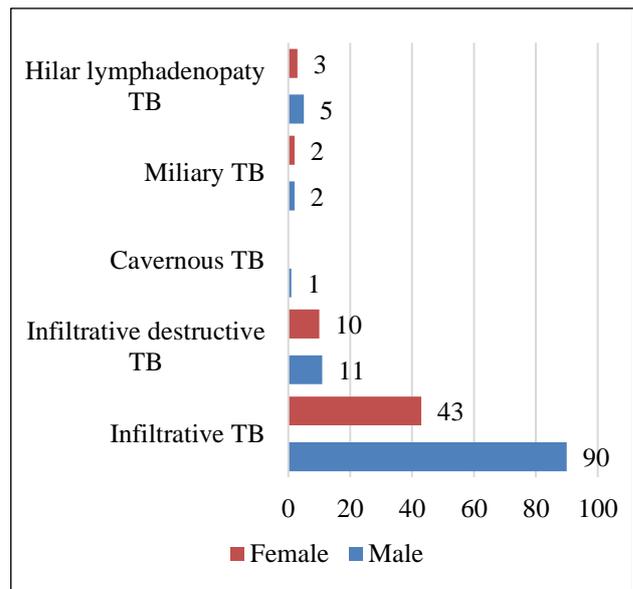


Figure 3: Patients according to the gender and diagnosis.

The period from the beginning of complaints in establishing the diagnosis was on average 65.5±57.9 days (from 2 to 300 days), most often between 22-60 days.

After the hospitalization, the period of establishing the final diagnosis of TB was 7±4 days (from 2-40 days). In 106 (63.5%) patients, the diagnosis was confirmed in ≤ 7 days, in 57 (34.1%) after 8-14 days of hospitalization. The average day of patients' hospitalization was 18.8±10.5 (from 1 to 90 days), the majority - 80 (47.9%) patients of 16-30 days, 51 (30.5%) - 8 to 15 days, 19 (11.4%) - over 30 days and 17 (10.2%) ≤7 days.

Endoscopic presentation (Figure 4) resulted normal in 7 (4.2%) patients examined, with signs of nonspecific bronchitis - 60 (35.9%) cases, edematous -hyperemic - 62 (37.1%), caseous inflammation - 7 (4.2%), ulcerative lesions - 3 (1.8%), tumoral lesions - 21 (12.6%) and fibrous stenotic changes - 7 (4.2%) patients. In relation to gender, the visible endobronchial changes were observed with a relative frequency greater in women (M = 109/F = 58) for caseous lesions 1.8% to 8.6%, for fibrous stenosis lesions - 3.7% to 5.17% and tumoral lesions 10.1% to 17.2%.

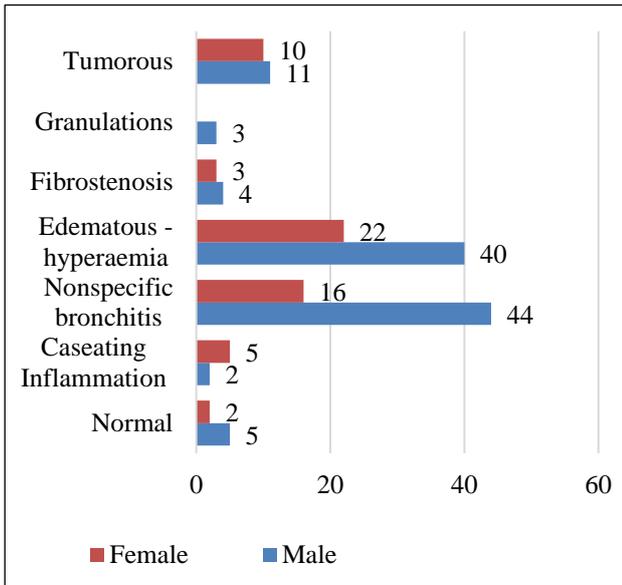


Figure 4: Patients according to the gender and endoscopic results.

Out of 44 patients in which it was obtained biopsy (26.3% of 167 total patients or 27.5% of 160 fiberoptic bronchoscopies where are noticed pathological lesions) have resulted in 24 (54.5%) cases with TB granuloma in histological examination, 14 (31.8%) cases with epithelioid granulomas and in 6 (13.6%) cases with non-specific inflammation (Figure 5).

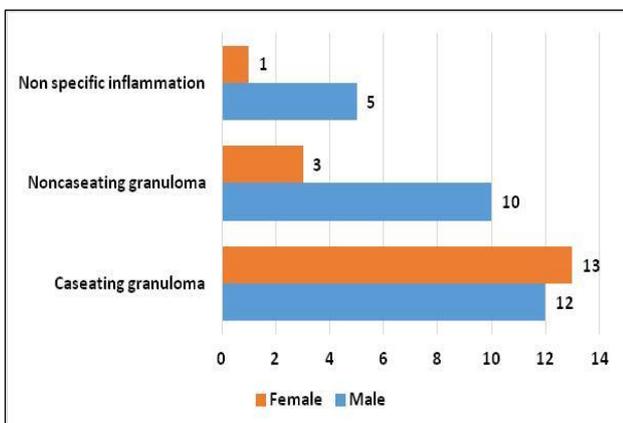


Figure 5: Patients according the gender and histopathologic results.

The examination of bronchial washing for Acid-fast bacillus smear concluded the diagnosis in 40.4% of cases, the examination for acid-fast bacillus smear collected after diagnostic FBS was decisive in 53.9% of cases. The examination for acid-fast bacillus culture resulted positive in 70.5% of bronchial washing and in 61.2% of sputum collected after FBS.

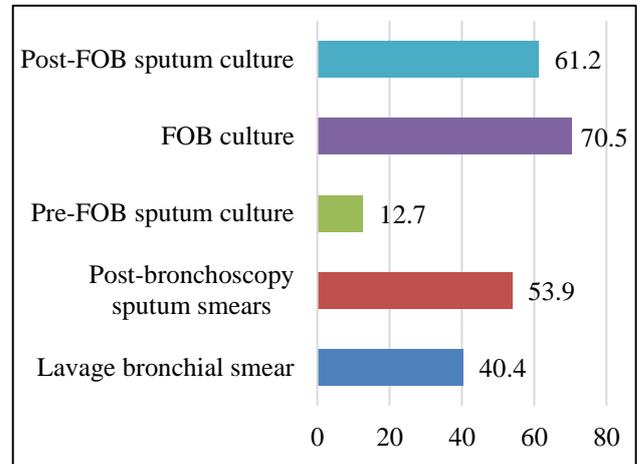


Figure 6: AFB smears and cultures results (%).

But in 27 (16.2%) cases of patients in the study has not resulted positivity for AFB in any of the procedures. In these cases, the diagnosis was based on histological data: 3 patients from biopsy material - with TB granulomas; in 2 patients, the TB diagnosis is based on histological results with epithelioid granuloma; and in one of these patients resulted the histological examination a nonspecific inflammation. In 22 (13.2%) cases without bacteriological or histologically confirmed diagnosis, the diagnosis is based on anamnesis, clinical-radiological features, and is confirmed from evaluation of the disease after specific antitubercular treatment.

DISCUSSION

The results of the study show that in 45.5%, the admission diagnosis in the hospital was pulmonary tuberculosis. In other patients, the wrong diagnosis was for pneumonia, but the disease that requires differentiation is pulmonary neoplasia.

In study, related cases about 20% have presented atypical radiological features. Chest radiography is another method commonly used in detecting PTB, but in many cases with AFB smear negative, x-ray findings are atypical or normal.¹⁵ In addition, this examination has the limitation of a high degree of false positivity due to previous PTB infection in an area with intermediate or high TB incidence.

In almost all patients, endobronchial changes have been observed, but with predominance of non-specific TB changes. This is also found in the literature, where the most common bronchoscopic finding was congestion

with moderate hyperemia and variable size white plaques. In all patients with cavitation lesions, mucosa was ulcerated and swollen.¹⁰ According to Panda et al, bronchoscopic appearance of bronchial mucosa was normal in 44% of cases, 21% had abnormal granular mucosa, 35% had bronchial mucoid secretions, 5% had tumor like growth, 3% had external compression and 3% had bronchial hemorrhage, and in some cases, there have been multiple lesions.¹⁶

According to a study in our country, the occurrences of chronic bronchitis (36.5% - atrophic bronchitis and 6.8% hypertrophic bronchitis) prevail in the non-specific changes, considering, moreover, that most of the patients were smokers (89%).¹⁷

In relation to gender, it has been shown that the endobronchial lesions have the largest relative frequency in women, which also corresponds to the literature data. Classically, endobronchial TB was considered a disease of young women.¹⁹ However, in the Golshan study, male patients are affected twice as often as women, which is consistent with several studies.^{18,20}

In most tuberculosis centers, even after meticulous research, positive bacteriological results from sputum at about 16 to 50% and a large part of the results remain negative and since the clinical profile and radiological lesions were consistent with the diagnosis of Pulmonary tuberculosis.⁹ Sputum culture for *M. tuberculosis* takes a long time and a reliable serological test is not yet available. In such situations bronchoscopy has been judged for the rapid diagnosis of tuberculosis. The fiberoptic bronchopulmonary smear examination of bronchial washing, including the culture for *Mycobacterium tuberculosis*, has a key role to play in diagnosing when smear negative repeatedly, when sputum expectoration is missing or sputum induction has failed.

Our enrolled cases were sputum smear negative to three sputum specimens examination. Positivity in the detection of *Mycobacterium tuberculosis* in the cases found in the study results is evidenced in 12.7% of cases with culture prior to performing fibroscopy, at hospital admission, at 40.4% with smear examination of bronchial washing, at 70.5% with culture of bronchial washing, 53.9% with the smear examination of sputum collected after FBS and 61.2% with cultured of sputum collected after FBS.

The use of FBS for the diagnosis of TB has been demonstrated in multiple studies.²⁰⁻²² The diagnostic usefulness is seen between 11% and 96%; (20, 21, 22) being exclusively diagnostic in 2% to 52% of cases and providing immediate diagnosis in 4% to 79% of cases.²⁰⁻²² This wide range of values may be because these studies are from different geographic areas where TB prevalence is different. In a larger retrospective study of 144 patients

with pulmonary TB from IP et al, 125 patients were diagnosed through FBS, i.e. about 87% of cases.²⁰

The culture for *Mycobacterium tuberculosis* from transbronchial biopsy has been found to have little use, and this was not seen as a source of positive culture material in every patient.^{23,24} BAL diagnostic result for *Mycobacterium tuberculosis* is higher compared to bronchial washing.²⁵ An explanation for this observation is the lower concentration of lidocaine in bronchoalveolar lavage compared to bronchial washing. Local anesthetics such as tetracaine and lidocaine used in the bronchoscopy inhibit the growth of *Mycobacterium tuberculosis* and other bacteria.^{26, 27}

In 44 patients with obtained bioptic material (26.3% of the total of 167 patients) resulted 24 patients (54.5%) - TB granuloma, 14 patients (31.8%) - epithelioid granuloma and 6 patients (13.6%) - nonspecific inflammation. Patients with histological examination has resulted TB granuloma in all cases with TB cavernous, 4/6 patients (66.6%) in TB adenopathy, 8/13 (61.5%) patients with TB infiltrative destructive, 11/22 (50%) patients with TB infiltrative.

From the combination of the positive results of bronchial washing smear and histopathology, the diagnosis was set at 48.3% in the Bachh study, while it was 48 and 50% in the studies performed respectively by Wallace et al and Kulpati et al.^{5,9,10} If granulomatous inflammation is also recognized as sufficient evidence for early tuberculosis diagnosis, the diagnostic achievement in the Bachh study is 61.6% compared to 75% in the study by Danek and Brower.^{10,28}

In present study, the positive result of smear examination in the bronchial washing was much higher in cases where histopathology of the bioptic material resulted TB granuloma. Anatomy-pathological examination of bioptic material can immediately establish diagnosis of tuberculosis as well as it helps determine the diagnosis of other diseases with different etiologies. Thus, based on the *M. Tuberculosis* positivity of the cases in the study it results that for rapid confirmation it helps in 40.4% of cases with smear examination of bronchial washing and 53.9% of cases with sputum smear examination collected after FBS. Positive culture results are achieved in 70.5% from the bronchial washing and in 61.2% from the sputum collected after FBS.

According to a study total yield of bronchoscopy in diagnosis of sputum smear negative pulmonary tuberculosis was 83.33% (50/60); bronchoscopy was the only diagnostic method in 66% cases (40/60) with bronchial washings being the only diagnostic method in 48.33%.¹⁰ Bronchial washings smear for AFB and histopathological evidence of caseating granuloma made immediate diagnosis possible in 48.33% (29/60) patients.

Fibro bronchoscopy provides material for early diagnosis e.g. bronchial washing smear examination, endobronchial and transbronchial biopsy for histopathological study. In the Bachh study bronchial washing smear was positive in 35% of patients; these were confirmed by positive culture.¹⁰ Danek and Bower and Purohi et al, demonstrated *M. tuberculosis* in 34% and 42% respectively, while in the study by Kulpati et al, were positive in 40%.^{9,28,29}

Examination of post-bronchoscopy sputum provides additional confirmation in cases of sputum smear negative pulmonary tuberculosis. In various previous studies, the fiber optic bronchoscope in combination with transbronchial lung biopsy has reached the early diagnosis in 60% - 85% of smear negative pulmonary tuberculosis.¹⁰

The diagnostic ability achieved by culture was also significantly higher in combination of the first and second bronchial washing specimens compared to the first bronchial washing. (total cases: 163 (94%) versus 141 (81%), $p < 0.001$; cases for smear negative sputum: 86 (91%) versus 73 (77%), $p < 0.001$; cases for poor expectoration: 77 (98%) versus 68 (86%), $p = 0.004$).³⁰ Obtaining an additional bronchial washing sample may be a useful alternative and to be considered for the diagnosis of TB in patients with smear negative sputum or who cannot produce sputum samples.³⁰

The positive predictive value of smear examination for diagnosis of pulmonary tuberculosis resulted from 60-70% for samples taken from induced sputum and BAL.³¹⁻³² If the bronchoscopy is performed, because it is a procedure that induces the cough, additional sputum samples for smear and culture should be collected after the procedure to increase the diagnostic yield.

In 27 (16.2%) cases of patients in the study no *M. Tuberculosis* positivity was achieved in any of the procedures. In these cases, the diagnosis was based: on 3 patients from the histological result of the bioptic material-tuberculous granuloma; in 2 patients, tuberculosis diagnosis was supported by epithelioid granuloma; and in one of these patients' histologic examination resulted in non-specific inflammation. In 22 (13.2%) patients without bacteriological or histologic confirmation, the diagnosis was based on anamnestic, clinical and radiological presentation, as well as confirmed by positive response to the application of treatment regimens.

CONCLUSION

Bronchial wash with bronchoscopy is a valid examination for rapid diagnosis of tuberculosis in cases of sputum smear negative. Endoscopic appearance has often resulted non-specific. Endobronchial lesions, especially caseous one, have a much greater relative frequency in women. Histopathological examination is an additional method

available in diagnostic confirmation, especially, in differentiation from pulmonary neoplasia.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Peposhi IP, Kapisyzi PQ, Hafizi HS, Bala SA, Nuredini OG. Value of bronchoscopy in the diagnosis of sputum smear negative pulmonary tuberculosis. Int J Res Med Sci 2017;5:3393-9.