The diagnostic value of bronchoscopy in smear negative cases with pulmonary tuberculosis

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ÖZET

Yayma negatif pulmoner tüberkülozlu olgularda bronkoskopinin tanısal değeri

Pulmoner tüberküloz şüphesi olduğu halde balgam yayması negatif olan olgularda bronkoskopinin yararlı olduğunu gösteren çok sayıda çalışma bulunmaktadır. Ancak hangi olgularda bronkoskopinin daha yararlı olduğu konusunda yeterli veri bulunmamaktadır. Bu çalışmada hangi olgularda bronkoskopinin daha fazla tanı koydurucu olduğu, hangi olgularda endobronşiyal tutulumun daha fazla bulunabileceği araştırıldı. Bu amaçla tüberküloz şüphesi olan, balgam incelemesinin negatif olduğu 60 olguya bronkoskopi yapıldı. Tüberküloz tanısı konulan olgulardan bronkoskopi ile tanı konulan ve konulamayan olgular ile endobronşiyal tüberküloz belirlenen ve belirlenemeyen olguların özellikleri karşılaştırıldı. Bronkoskopi ile sonradan tüberküloz tanısı doğrulanan 38 olgunun 29 (%76)'una tanı konuldu. Olguların 7 (%18)'sinde de endobronşiyal tutulum tespit edildi. Bronkoskopi ile tanı konulan olguların ortalama serum C-reaktif protein (CRP) düzeyleri tanı konulamayan olgulara göre anlamlı derecede yüksekti (p< 0.05). Endobronşiyal tutulum olan olgular diğer olgularla karşılaştırıldığında da bu olgularda semptom süresinin daha kısa (p= 0.01), tüberkülin deri testi (TDT)'nde endürasyon çapının daha küçük (p< 0.05) ve ortalama serum CRP düzeyinin daha yüksek (p< 0.05) olduğu görüldü. Çalışmanın sonuçları yüksek serum CRP düzeyi olan olgularda bronkoskopi ile tanı konulma olasılığının daha fazla olduğunu; TDT yanıtının oluşmadığı, semptom süresinin kısa olduğu ve CRP düzeyinin yüksek olduğu hastalığın erken ve aktif döneminde endobronşiyal tutulumun tespit edilme olasılığının daha fazla olduğunu düşündürmektedir. Ancak bu hipotezin desteklenmesi için yeni ve daha büyük çalışmalar gereklidir.

Anahtar Kelimeler: *Bronkoskopi, tanı, endobronşiyal, pulmoner, tüberküloz.*

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There are many studies showing usefulness of bronchoscopy in patients with suspected pulmonary tuberculosis (Tbc) and negative sputum smear. However, there is no enough data concerning that in which cases bronchoscopy is more useful. We aimed to investigate in which cases bronchoscopy is more diagnostic and also an in which cases presence of endobronchial involvement is more likely. A total of 60 smear negative patients undergoing bronchoscopy due to tuberculosis suspicion were evaluated. The characteristics of cases with or without positive diagnosis via bronchoscopy and also of the ones with or without endobronchial involvement were compared. Bronchoscopy provided positive result for Tbc in 29 (76%) of 38 cases with confirmed as Tbc later and 7 (18%) cases had endobronchial involvement. In the cases who are diagnosed as Tbc via bronchoscopy, the mean serum levels of C-reactive protein (CRP) were significantly higher than those of undiagnosed (p< 0.05). In the cases with endobronchial involvement, the duration of symptoms was significantly shorter (p= 0.01); the diameter of tuberculin skin test induration was significantly smaller (p< 0.05); and mean serum level of CRP was significantly higher (p< 0.05) than those of without endobronchial lesion. The results suggest that it is more likely to diagnose Tbc bronchoscopically in the cases who had increased serum levels of CRP, and possibility of endobronchial involvement may be increased among the cases in active and earlier period of the disease. However, further studies are required to support this hypothesis.

Key Words: Bronchoscopy, diagnosis, endobronchial, pulmonary, tuberculosis.

Tuberculosis (Tbc) is one of the most important health problems worldwide (1). An effective program to control Tbc includes early diagnosis of the disease. The gold standard for the diagnosis of Tbc is bacteriologic confirmation. Freshly expectorated sputum in cases with pulmonary Tbc (PTbc) is the best sample to stain and culture for *Mycobacterium tuberculosis*. However, obtaining diagnostic material is not always possible, especially in patients who are unable to expectorate sputum, or the achieved material may be nondiagnostic. In such cases, either the diagnostic material is achieved by induced sputum or bronchoscopy, or the diagnosis was made by combination of clinical findings and/or after a successful therapeutic trial (2).

Flexible fiberoptic bronchoscopy (FFB) has been shown to be useful tool for the diagnosis of Tbc, even in the cases who had negative acid-fast bacilli (AFB) in sputum smear. When sputum analyses are unfruitful, bronchoscopic procedures such as brushings, transbronchial biopsy, or needle aspiration can provide diagnostic material (3-8). Another important advantage of bronchoscopy is its usefulness in the evaluation of an endobronchial involvement of Tbc, which is also called endobronchial Tbc (EBTbc). EBTbc is the most often complication of primary PTbc in children; however, it may also occur in adults (9). Although Tbc is usually limited to lung parenchyma, the clinical manifestations of Tbc are quite variable and depend on a number of factors, such as age and immune status of host or virulence of the organism (10).

There are many studies showing usefulness of bronchoscopy in patients with suspected PTbc with negative sputum smear, but there is no enough data concerning that in which cases FFB was more useful and EBTbc was most likely to occur? (3-8). Thus, this study was aimed to in-

vestigate the contribution of FFB in the diagnosis of suspected PTbc cases with negative sputum smear and to evaluate clinical characteristics of the cases with EBTbc.

MATERIALS and METHODS

Patients

Prospectively, the cases with PTbc suspicion, due to respiratory complaints or/and radiological findings, were included in the study for consecutive four years. Sputum specimens, spontaneous and/or induced, of the cases with suspected respiratory symptoms and radiological findings compatible with PTbc were collected for three consecutive days. After exclusion of the cases with positive results, the remaining 70 cases with negative results or without sputum production evaluated. Some of the cases were also excluded from the study because of without spu-

tum (n= 5), any contraindication to or no consent for FFB (n= 5) or another diagnosis (n= 22) after bronchoscopy. Finally 38 cases, in whom smear negative and the Tbc diagnosis was confirmed later, were included in present study. The diagnostic algorithm of the cases was shown in Figure 1. Demographic, clinical, radiological and laboratory data of the cases were recorded. Written informed consent of all patients was obtained and, study protocol was approved by local ethic committee.

Smear negative cases were defined to the following criteria: At least three sputum specimens negative for AFB, radiographic abnormalities consistent with active PTbc, and no response to a course of broad spectrum antibiotics, and decision by a clinician to treat with a full course of anti-Tbc chemotherapy (11).
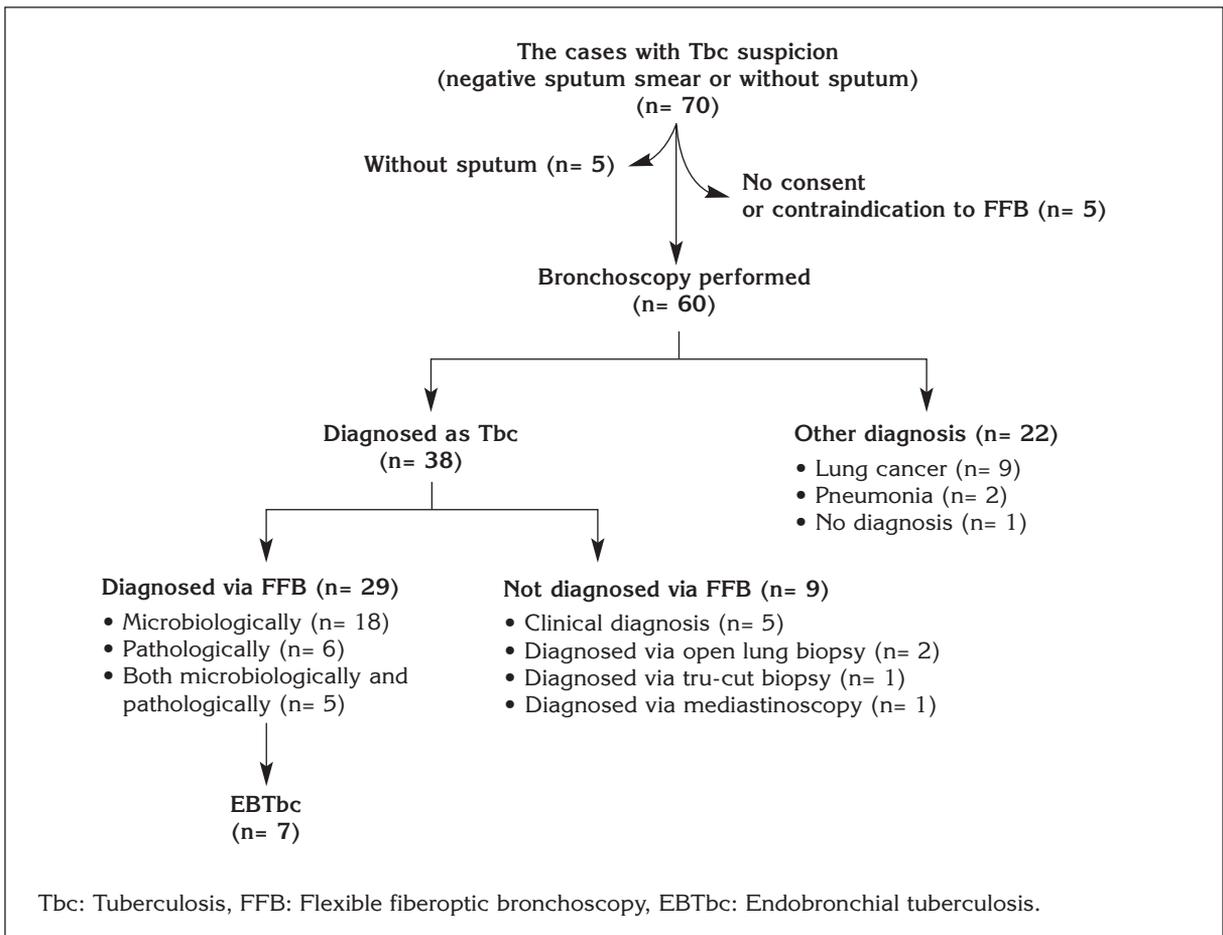

Figure 1. Diagnostic algorithm of the cases.

Diagnostic Procedures

In addition to routine laboratory tests, tuberculin skin test (TST) and human immunodeficiency virus (HIV) test were also performed. All cases had equal to or less than two scars of Bacille Calmette-Guérin (BCG) vaccine. All enrolled patients underwent FFB in 24-48 hours after the smear results were obtained. Bronchoscopic lavage (BL) and postbronchoscopic sputum (PBS) were taken from all cases. In addition, biopsy from lesion in the cases with endobronchial lesion, at least three biopsy, and transbronchial lung biopsy (TBLB) in the cases with miliary pattern on chest X-ray were taken. The cases were aso classified into three groups according to the degree of lung involvement as assessed by chest X-ray: Mild (n= 22), a single lobe involved without any cavity; moderate (n= 12), two or more lobes involved or cavitary disease; or advanced (n= 4), bilateral disease with or without cavitation.

In the cases who had no diagnosis after FFB either treated empirically by considering Tbc or more invasive diagnostic approaches such as mediastinoscopy, tru-cut biopsy or open lung biopsy were performed. In the cases with EBTbc, a control with FFB was planned at five months of follow-up.

All specimen were digested and decontamined by the sodium dodecyl sulphate-NaOH method and then centrifuged. Smears of sediment were stained with Ziehl-Neelsen staining. Mycobacterial cultures were performed by sample inoculation onto a Loewenstein-Jensen slant. Biopsies were stained with hematoxylin and eosin and Ziehl-Neelsen staining. Biopsies were considered positive of caseating granulomas or AFB (or both) was present.

Statistical Analysis

Data were analyzed using the SPSS version 11 statistical software (SPSS Inc., Chicago, IL). Correlation between radiological extent of disease and CRP levels was calculated using Spearman's rank order correlation coefficients. Pearson's Chi Square test and Mann Whitney U test were used analysis of categorical variables and continuous variables, respectively. Data expressed as the mean ± SD and a probability test less than 0.05 was considered to be statistically significant.

RESULTS

A total of 38 patients including 26 males and 12 females were included in the study. The mean age of the patients was 38 ± 16 years (range 19-74). The results of all cases for HIV test were negative. As shown in Figure 1, bronchoscopy provided a positive result for Tbc in 29 (76%) cases. Out of them, 18 cases were diagnosed only microbiologically (i.e. positive BL and/or PBS smear), six cases only pathologically and five cases both pathologically and microbiologically. Of the cases who were diagnosed pathologically via FFB (n= 11), 7 (18%) had an endobronchial lesion (EBTbc) and the remaining four had positive result on TBLB. The diagnosis of nine cases, in whom bronchoscopy did not provide positive result, were established with open lung biopsy (n= 2), mediastinoscopy (n= 1), tru-cut biopsy (n= 1), and clinical diagnosis (n= 5) (Figure 1).

The mean serum C-reactive protein (CRP) level was significantly higher in cases who were diagnosed by FFB when compared to the cases who were not diagnosed by FFB (3.2 ± 5.9 mg/dL vs. 1.7 ± 1.5 mg/dL, $p < 0.05$). Also CRP levels were well-correlated with the extent of disease ($r = 0.24$, $p < 0.05$). Although there were some differences among the other parameters, they were not statistically significant (Table 1).

In the cases with EBTbc, the duration of symptoms was significantly shorter ($p = 0.01$); the diameter of TST induration was significantly smaller ($p < 0.05$); and mean serum level of CRP was significantly higher ($p < 0.05$) than those of without EBTbc (Table 2).

Of cases with EBTbc, three had mediastinal lymphadenomegaly, two exudative lesions, one cavitary lesion and one no lesion on chest X-ray. In bronchoscopy, diffuse mucosal congestion edema was the most common finding (n= 4).

Table 1. The characteristics of all cases.*

	With positive result (n= 29)	With negative result (n= 9)	p
Demographics			
Gender (male/female)	20/8	6/4	0.51
Age	37 ± 15	39 ± 17	0.66
Clinical characteristics			
Symptom duration (month)	3.7 ± 4.8	5.9 ± 6.8	0.33
Cough	21	6	0.36
Sputum	13	4	0.59
Dyspnea	9	5	0.39
Chest pain	7	6	0.07
Haemoptis	2	1	0.81
The diameter of TST induration (mm)	17 ± 5	15 ± 6	0.58
History of an associated disease	4	1	0.92
Radiological localization			
Bilateral	6	2	0.42
Upper zone	10	8	0.27
Laboratory findings**			
CRP (mg/dL)	3.2 ± 5.9	1.7 ± 1.5	**0.04**
Sedimentation rate	41 ± 34	28 ± 18	0.15
LDH	460 ± 184	390 ± 194	0.32

* Data are presented as mean ± SD unless otherwise indicated.

** The usual symptoms and routine laboratory findings of the cases were not included in the table because of nonspecificity.

TST: Tuberculin skin test, CRP: C-reactive protein, LDH: Lactat dehydrogenase.

Table 2. The characteristics of the cases with endobronchial lesion.*

	With endobronchial lesion (n= 7)	Without endobronchial lesion (n= 31)	p
Demographics			
Gender (male/female)	5/2	21/10	0.27
Age	35 ± 11	39 ± 17	0.54
Clinical characteristics			
Symptom duration (mo.)	1.7 ± 0.5	4.6 ± 5.8	< 0.01
The diameter of TST induration (mm)	13 ± 4	18 ± 5	< 0.05
Cough	4 (57%)	23 (74%)	0.37
Sputum	2 (29%)	15 (48%)	0.34
Dyspnea	1 (14%)	13 (42%)	0.17
Chest pain	4 (57%)	9 (29%)	0.15
Hemoptysis	1 (14%)	2 (6%)	0.49
Co-morbid disease	0 (0%)	5 (16%)	0.77
Radiology			
Bilateral	1 (14%)	7 (23%)	0.57
Upper zone	4 (57%)	14 (45%)	0.69
Laboratory findings**			
CRP (mg/dL)	8.6 ± 5.3	1.37 ± 1.16	< 0.05
ESR (mm/hour)	29 ± 24	38 ± 33	0.49
LDH (U/mL)	325 ± 41	447 ± 199	0.09

* Data are presented as mean ± SD or n (%) unless otherwise indicated.

** The usual symptoms and routine laboratory findings of the cases were not included in the Table because of nonspecificity.

TST: Tuberculin skin test, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactat dehydrogenase.
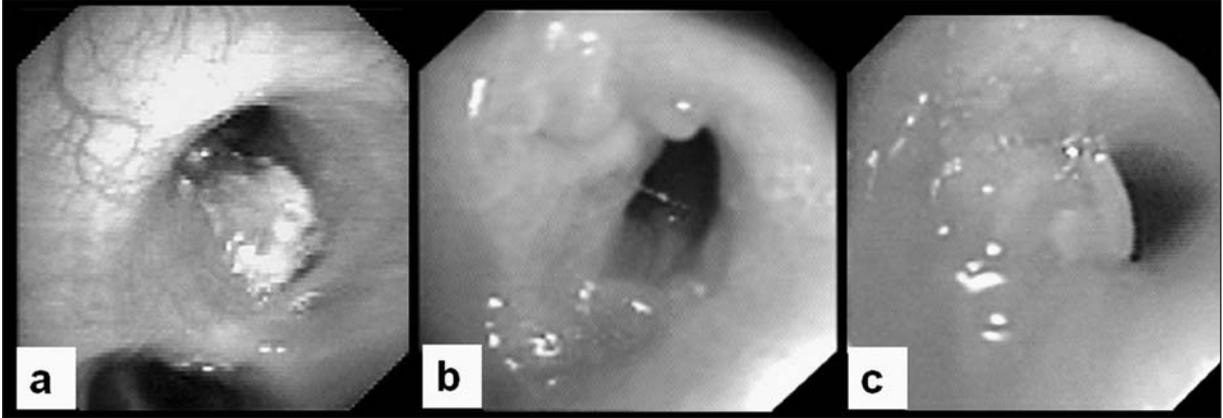
Figure 2. Examples of endobronchial involvements: (a) necrotic, (b) nodular and (c) edematous lesions of bronchial mucosa.

Figure 3. Bronchoscopic imagings of endobronchial involvement of the case with mediastinal lymphadenopathy (a) before and (b) after the treatment.

Other bronchoscopic findings included endobronchial lesion (n= 3), ulceration (n= 2) and mucosal nodularity (n= 1) (Figure 2). Follow-up bronchoscopy after five months, which was performed in four of the cases, showed that EBTbc was almost recovered (Figure 3).

DISCUSSION

In a suspicion of PTbc, AFB investigation in the sputum is the most useful method for making a prompt Tbc diagnosis. Sometimes sputum may not be expectorated or may be nondiagnostic. In most circumstances, induced sputum is used as a first alternative diagnostic tool due to its noninvasiveness and low cost. However, it may be nondiagnostic also. In such conditions, an empirical anti-Tbc treatment may be initiated (12); however, bronchoscopy may sometimes be required to obtain specimen not only confirm tuberculosis diagnosis but also rule out other pos-

sible diagnosis. Diagnostic value of FFB in the diagnosis of PTbc has been shown in the previous studies (3-8). There are also new attempts to increase diagnostic success of FFB by combining use of bronchoalveolar lavage and PCR (13). In our study, bronchoscopy was diagnostic in majority of cases (76%), especially in the cases with increased serum levels of CRP, without any complication. The increase of serum levels of CRP has been shown to be associated with the disease severity (14). Thus, increased diagnostic rate of bronchoscopy may be associated with the severity of the disease in such cases.

Bronchoscopy not only contributes to diagnosis of pulmonary tuberculosis but also useful in the differential diagnosis of tuberculosis with the diseases commonly encountered in clinical practice such as pneumonia or lung cancer. Although some clinical parameters or new serological

approaches may be helpful in the differential diagnosis of the diseases, it is clear that bronchoscopic evaluation and interventions are still more useful tools for this aim (15). In addition to diagnostic value of FFB, it was also revealed presence of EBTbc in 7 (18%) cases. The pathogenesis of EBTbc is not yet fully established. However, possible mechanisms of the development of EBTbc include direct implantation of mucosal surface of tubercle bacilli into the bronchus from adjacent pulmonary parenchymal lesion, direct airway infiltration from an adjacent tuberculous mediastinal lymph node, erosion or protrusion of an intrathoracic tuberculous lymph node into the bronchus, hematogenous spread, and extension to the peribronchial region by lymphatic drainage (16,17). In our study, mediastinal lymphadenomegaly was the most common chest X-ray finding in the cases. Tuberculous mediastinal lymphadenopathy may sometimes show an atypical clinical manifestation, and it has been shown that it may be associated with EBTbc (18,19).

There are many reports of EBTbc either large series or case reports with or without atypical manifestations (10,14-23). EBTbc has been found in patients both with and without AFB positivity. However, the proportion of AFB positivity shows some differences between studies. While AFB is positive only nine of 102 cases with EBTbc in the study of Lee et al., the AFB positive cases in the study of Chung HS et al. were in 57 of 107 patients (17,20). Because the conflicting results, it is difficult to discuss any association between EBTbc and AFB positivity. On the other hand it is not necessary to perform bronchoscopy in the cases with positive AFB without any other concomitant disease, such as malignity, suspicion.

Chest X-ray finding of the cases with EBTbc either may have different pathological pattern or may be normal. In our cases with EBTbc, chest X-ray findings included, in decreasing order, mediastinal lymphadenomegaly, exudative lesions, cavitary lesion and no abnormality. Although most of our cases had a pathological finding on their chest X-ray imaging, the proportion of cases with normal chest X-ray may be fairly higher as stated in the studies above mentioned (20,22). The difference may be due to the characteristics of our study population, such as small size and not including AFB positive cases.

Other interesting findings of the study were increased serum levels of CRP, shorter symptom duration and smaller diameter of TST induration in the cases with EBTbc. These findings suggest that in EBTbc may be an early finding of active Tbc, in which TST response is not sufficiently occurred. Another possible explanation for TST negativity may be less reactivity of the cases with EBTbc. Because our cases had less than or equal to two BCG vaccine scar and it is considered that the effect of BCG vaccination generally wanes with time and a positive TST is not recommended to be attributed to the vaccination after a five years duration since the last BCG vaccination, our results were not considered to be associated with BCG vaccination (24). The clinical course of EBTbc is variable because of several possible pathologic mechanisms and the complex interaction between the mycobacteria, host immunity and anti-Tbc drugs. It has been shown that the most serious complication of EBTbc is bronchostenosis, even in the cases who are treated adequately, and it is reported that its occurrence may vary according to the type of lesion (17,25-27). However, we did not experience any symptom or finding of bronchostenosis. Early diagnosis with bronchoscopy and appropriate treatment of EBTbc with anti-Tbc drugs (with or without steroids) may have a role in the prevention of the development of complications such as bronchostenosis. However, it needs further studies.

As a conclusion, bronchoscopy provides a substantial contribution to the diagnosis of Tbc. The results suggest that it is very likely to diagnose Tbc in the cases with negative AFB who had increased serum levels of CRP via bronchoscopy. EBTbc may be an early and diagnostic finding of active Tbc, even in the cases with negative AFB, mediastinal lymphadenopathy and normal chest X-ray.

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