Manuscript type: Original Article

DOI: 10.5152/TurkThoracJ.2018.180140

Title: Correlation Between Diagnostic Yield from Bronchoalveolar Lavage Fluid Analysis and Clinicoradiological Findings in Sarcoidosis

Short title: Bronchoalveolar Lavage in Sarcoidosis

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Received: 05.09.2018

Accepted: 18.10.2018

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Tokgöz Akyıl F, Ağca M, Öztürk H, et al. Correlation Between Diagnostic Yield from Bronchoalveolar Lavage Fluid Analysis and Clinicoradiological Findings in Sarcoidosis. Turk Thorac J 2018; DOI: 10.5152/TurkThoracJ.2018.180140

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Abstract

Objective: The diagnosis of sarcoidosis is challenging at most times, requiring a search for less-invasive, more reliable diagnostic methods. Bronchoalveolar lavage fluid (BALF) analysis has been used in the differential diagnosis of sarcoidosis for many years with a wide sensitivity and specificity rates. The objective of the study is to investigate whether diagnostic performance of BALF analysis is altered by clinicoradiological findings of sarcoidosis patients.

Material and Methods: The present study is a retrospective, single center, observational study designed in a sarcoidosis outpatient clinic in a training hospital. Patients who had undergone BAL procedure at diagnosis were included in the study. Demographics, clinical and detailed chest X-ray and high resolution computed tomography (HRCT) findings at diagnosis were recorded. According to diagnostic performance, BALF results were Grouped as `diagnostic` and `non-diagnostic` and recorded parameters were compared between the Groups.

Results: Of all the 257 patients' BALF analysis, the mean lymphocyte ratio was 41±17.5 (5-80) and the mean CD4/CD8 was 5.5±4.7 (0.1-24.7). BALF analysis was diagnostic in 56 % (n=145). Diagnostic performance of the procedure did not correlate with any of the demographics, smoking status,

spirometric findings, chest X-ray staging, HRCT findings and tomography scoring. Extra-pulmonary involvement was significantly more frequent in diagnostic group (66% vs. 34%, P=0.006).

Conclusion: BALF results signal sarcoidosis in more than half of the patients. The diagnostic role of BALF is greater in patients with extra-pulmonary involvement.

Keywords: bronchoalveolar lavage, lymphocytes, sarcoidosis

Introduction

Sarcoidosis is a chronic inflammatory disorder with an unknown cause affecting mostly the pulmonary and lymphatic systems[1].Diagnosis of sarcoidosis may be challenging and clinicians seek less invasive and morereliable diagnostic methods. Bronchoalveolar lavage fluid (BALF) analysis has been used in the generation of a differential diagnosis for many years. In sarcoidosis, unknown agents drive aTh1 immune response and CD4+ T lymphocytes migrate to affected tissues. As a result, lymphocytosis and altered CD4/CD8 ratios in BALF have been associated with a diagnosis of sarcoidosis [2,3].

To date, many studies have been published on the relationship between the use of BALF and the diagnosis of sarcoidosis. There is a high level of variability in terms of sensitivity, specificity and cut-off values for CD4/CD8 ratios [4,5-8]. Several factors, including radiographic stages, tobacco smoking and corticosteroid treatment, have been described as having an influence on BALF lymphocyte ratios and CD4/CD8 ratios [9-12]. Nevertheless, no systematic evaluation of the diagnostic performance of BALF analysis has been undertaken.

In this respect, we hypothesize that the extent and severity of airway inflammation can change clinical and radiological features, leading to variations in the diagnostic role of BALF in sarcoidosis. The aim of the present study is to investigate the diagnostic performance of BALF results according to baseline clinical and radiological features.

Material and Methods

The present study is a retrospective, single-centre, observational study, designed in a respiratory training and research hospital. Between September 2005 and September 2016, all patient records of sarcoidosis that presented to the outpatient clinic were investigated. Patients who had undergone a BAL procedure prior to diagnosis and had sufficient medical data and radiological images at diagnosis were included. Patients with insufficient medical data, incomplete BALF results and inconvenient BAL performances were excluded (Figure 1). Ethical committee approval was obtained from the local research committee (12.10.2016: No:3) and verbal informed patient consent was approved by all patients. All patients were diagnosed and followed by expert pulmonologists.

Organisation of the sarcoidosis outpatient clinic

The hospital has a sarcoidosis outpatient clinic for patients that have been pre-diagnosed or diagnosed with the disease. The clinic implements a routine follow-up programme and clinical filing. BAL is carried out in compliance with published guidelines [13,14] using a flexible bronchoscope (Olympus BF, Type 1T160 or P160, Olympus, Tokyo, Japan) in the area of the most marked radiological abnormality seen on computed tomography, or in the case of diffuse involvement, the middle lobe or lingual is used. At least six aliquots of 20 mL sterile saline is instilled through the bronchoscope, and retrieved gently by suction.

Diagnosis is also carried out in line with published guidelines [15]. Once a patient is diagnosed as having sarcoidosis, serum and urine calcium levels, eye examination, echocardiographic and electrocardiography, and abdominal ultrasonography are routinely performed. If the patient has symptoms suggestive of involvement of any other system, this is evaluated in line with the disease involvement procedure [15].

Data collection and study design

Patient demographic and clinical data were collected. Diagnoses were re-evaluated by current guidelines [15]. Baseline spirometric findings and serum Angiotensin converting enzyme (ACE) (U/L) and serum calcium (mg/dl) levels were recorded. Chest X-ray grading at diagnosis were classified according to the Scadding system [16]. Baseline high resolution computed tomography findings were evaluated by a radiologist who was blinded to the medical history of the patient, according to the scoring system proposed by Oberstein et al. and then used in the study of Drent et al. [2,17]. Lung parenchyma involvement was evaluated qualitatively as bronchovascular bundle, intra-parenchymal nodules, septal and nonseptal lines, and parenchymal consolidation (including ground-glass opacities). The lung volume affected was quantified using a visual score as follows: 0=no lesions; 1=up to 33%; 2=up to 66%; and 3=more than 66% of the volume affected. Similarly, quantification of focal pleural thickening (PL) and enlargement (with a short axis of 1 cm or more considered enlarged) of the lymph nodes (LN), respectively, was carried out as follows: 0=no pathological findings; 1=minor; 2=moderate; and 3=pronounced changes. The total score was calculated.

The presence of any extrapulmonary involvement at the time of diagnosis was recorded.

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BALF results were recorded and grouped either as diagnostic or non-diagnostic. Diagnostic BAL was defined as a combination of ≥15% lymphocyte and >3.5 ratio of CD4/CD8 lymphocytes (14). According to the BALF results, patients were divided into 2 Groups: diagnostic and non-diagnostic. The baseline clinical and radiological findings were compared between Groups.

Statistical Analysis

Quantitative data are expressed as mean±standard deviation (SD) and qualitative data are expressed as frequencies. Student's t-test and chi-square tests were used for comparison. All statistical analyses were carried out using a statistical software package (SPSS for Windows, version 16.0; SPSS Inc.; Chicago, IL, USA). A P value of <0.05 was considered significant.

Results

Of all the 257 patients, 80 (31%) were male and the mean age was 42±12 years (18-78). Only 25% of the patients had ever smoked (Table 1). At presentation, chest roentgenograms were mainly classified as stage 1 (56%). The mean forced vital capacity (FVC) was 88±14% and carbon monoxide diffusing capacity (DLCO) was 79±18%. HRCT findings demonstrated bronchovascular bundles in 34% and parenchymal nodules in 56% of the patients. The average lymph node diameter of the largest lymph node was 15.7±5.6 mm. The mean radiographic total score was 6.2±3 (0-17).

Any extrapulmonary involvement was recorded in 65 (25%) patients. The most frequent involvement was dermatologic (N=48, 19%). The eye was affected in 13 patients. Cardiac, neurological, gastrointestinal involvement and hypercalcemia was recorded in 2 patients. BALF analysis revealed an average lymphocyte percent of 41±17.5 (5-80) and the average CD4/CD8 ratio was 5.5±4.7 (0.1-24.7). Lymphocytes were higher than 15% in 233 (91%) of the patients whereas the CD4/CD8 ratio

was greater than 3.5 in 152 patients (59%). BALF was evaluated as diagnostic in 145 (56%) patients (Table 1). Final diagnosis was made by clinical and radiological findings in 68 (26%) and histopathologically confirmed in 189 (74%) patients. Mediastinoscopy was diagnostic in 65 (25%), transbronchial biopsy in 58 (23%), endobronchial mucosa biopsy in 35 (14%), video assisted thoracoscopic surgery in 12 (5%), endobronchial ultrasonography in 14 (5%), peripheral lymph node or skin biopsy in 5 (2%) patients. BALF findings were diagnostic in 88 (47%) histopathologically confirmed diagnosed patients whereas 84% of clinically diagnosed patients ($p<0.001$). The diagnostic performance of BAL analysis did not correlate with gender, age, smoking status, ACE levels and spirometric findings ($P>0.05$, Table 2). Detailed analysis of smoking status revealed that smokers had lower neutrophil ratios compared to non-smokers ($P=0.04$, Table 3). Chest radiography staging did not correlate with BALF analysis (Table 4). Neither radiologic staging nor tomography findings affected airway inflammation BALF results. BALF analysis was more frequently diagnostic in patients with extrapulmonary involvement ($P=0.043$) (Table 2).

Discussion

The present study confirms that BALF analysis was a useful diagnostic aid in more than half of the patients. The diagnostic performance of the procedure did not correlate with demographics and/or radiological findings. Extrapulmonary involvement at diagnosis is described as a signifier of the BAL procedure for the first time.

Efared et al. have evaluated the diagnostic value of BAL in interstitial lung diseases and have not found a statistically significant relationship between lymphocytes and CD4/CD8 ratios and diagnosis. However the authors have grouped all diagnoses into discrete groups and the study population was

relatively small [18]. A recent meta-analysis of 17 papers including 999 patients with sarcoidosis and 886 controls has reported that the BALF CD4/CD8 ratio by itself is not sufficient for diagnosis but is helpful in improving diagnosis along with other diagnostic factors [5]. An epidemiological data of Turkish patients revealed a BALF analysis of lone lymphocytic alveolitis of 34% [19]. In a recent epidemiological study in Portugal, 289 sarcoidosis patients underwent a bronchoscopy procedure and 246 also underwent BALF analysis. It revealed that 90% of the subjects had lymphocytosis and CD4/CD8 ratios were ≥3.5 in 60.9% [20]. In line with the literature, when investigated in terms of lymphocytosis and CD4/CD8 ratios alone, the current study had similar findings. In line with the literature, we propose that although BAL fluid analysis is not diagnostic by itself, overall, it is a valuable diagnostic aid for sarcoidosis diagnosis.

In healthy subjects, BALF consists predominantly of macrophages (approximately 80%) and 5-15% lymphocytes. Again, in healthy subjects, the CD4/CD8 lymphocyte ratio is 1.0 - 3.5, with average values ranging between 1.5 and 2.0 [13,14]. A number of variables have been described to affect BALF results. Smoking increases BAL macrophage and neutrophil counts and decreases lymphocytes, CD4+ cells and CD4/CD8 ratios [14,21,22]. Elderly subjects have been reported to have increased levels of lymphocytes and neutrophils and an elevated CD4/CD8 ratio in BALF [13,23,24]. In the current study, age and smoking status did not affect the diagnostic value of BALF. In smokers, BALF neutrophils were increased regardless of the diagnostic performance. Smoking and advanced age may alter bronchoalveolar cell ratios; however, this has no impact on the diagnostic role of BALF.

A recent study by Aleksoniene et al. evaluated the relationship between radiological, spirometric changes and BAL fluid cells in 80 newly diagnosed sarcoidosis patients. They stated that chest rontgenogram Scadding stages of I, II and III had similar BALF lymphocytes and CD4/CD8 ratios. In

smokers, CD4/CD8 ratios were found to decrease compared to the ratios of the nonsmokers. In addition, restrictive pulmonary function tests correlated with higher BALF lymphocyte counts [25]. Similarly, Urbanowski et al. reported that in 54 non-smoker sarcoidosis and 24 smoker sarcoidosis patients, smokers had lower percentages of lymphocytes in BALF [9]. In contrast to these studies, no correlation was observed between spirometric findings, smoking status and BALF results in the current study. Although newly diagnosed patients have been included in both studies, the present study has grouped BALF results as diagnostic and non-diagnostic. Novel investigations may be required to clarify these issues.

In a prospective study by Danila et al., 221 non-treated non-smoking sarcoidosis patients' BALF was analysed according to radiologic stages. A significant decrease in CD4/CD8 ratios with increased radiographic stages was observed. However, in all stages, the mean CD4/CD8 ratios were higher than 4 [11]. The current study did not find a statistically significant difference in diagnostic performance according to stages. It should be noted, however, in agreement with Danila et. al., that higher than usual CD4/CD8 ratios were found in all stages. BAL procedure is suggested to be guided by HRCT findings [26]. The decision for the localization of the procedure has been guided by radiological findings in the present study. However, it should be noted that tomography score did not influence diagnostic role of the procedure in present study. A recent study has revealed a BAL fluid correlation with HRCT findings and BALF findings in *mycobacterium avium* infection [27]. As for sarcoidosis, patients having widespread and minimal parenchymal involvement had similar diagnostic rates. The most probable reason that sarcoidosis is caused by systemic inflammation instead of infection. It should be kept in mind that patients with minimal or no pulmonary parenchymal involvement may also have diagnostic BALF results. Extrapulmonary involvement has been reported in 40-50% of

sarcoidosis patients [28,29]. In the current study, only a quarter of the patients had extrapulmonary involvement. Only patients who had undergone a BAL procedure were included, with the probable reason of lower ratios of patients having extrapulmonary involvement. The present study concludes that higher BALF diagnostic yields are obtained in patients with more extensive disease. The higher diagnostic performance was significant in CD4/CD8 ratios (Table 5). This may be due to excess T helper cell activity in the body and more excessive airway inflammation. In the literature, no such relationship has been described previously, and it may be the subject of future investigations.

The following limitations to this paper should be noted. First, it was a retrospective, single-centre study. Second, some of the diagnostic tests were not available for further analysis, such as carbon monoxide diffusing capacity. Third, only one radiologist evaluated the radiographic sections. Finally, almost half of the sarcoidosis patients had not undergone BAL procedure mostly because of the patients' reluctance for the procedure. The strength of this study, on the other hand, is its large study sample within a well-documented sarcoidosis outpatient clinic. Additionally, all patients were diagnosed and followed by expert pulmonologists.

In conclusion, BALF analysis supports a diagnosis of sarcoidosis in more than half of the patients. Diagnostic role does not correlate with demographics, rontgenographic staging or tomography findings. The diagnostic role of BALF is greater in patients with extrapulmonary involvement.

Acknowledgement: We would like to thank all colleagues in sarcoidosis outpatient clinic.

Conflicts of interest: There is no conflict of interest related to this paper.

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Table 1: General characteristics of the patients

Gender	
Male	80 (31%)
Female	177 (69%)
Age (years)	42±12 (18-78)
Smoking status	
Ever smoker	65 (25%)
Never smoker	192 (75%)
FVC (%) min max	88±14 (41-109)
DLCO (%)	79±18 (34-110)
ACE (U/L)	66±45 (5-360)
Ca (mg/dL)	9.6±0.7 (8,0-17,8)
Chest X-ray Stag	
0	3 (1%)
1	143 (56%)
2	97 (38%)
3	14 (5%)
Diagnostic method	
Histopathological confirmed	189 (74%)
Other	68 (26%)
BALF analysis	
Lymphocyte %	41±17.5 (5-80)
Neutrophil %	16.6±9.7 (3-80)

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Eosinophil %	2.5±1.6 (0-12)
Macrophage %	40.7±17(2-83)
CD4/CD8	5.5±4.7 (0.1-24.7)
Diagnostic yield of BALF	
Diagnostic	145 (56%)
Non-diagnostic	112 (44%)
Extrapulmonary involvement	
Present	65 (25%)
Absent	192 (75%)

ACE: angiotensin converting enzyme, BALF: bronchoalveoler lavage fluid, Ca:calcium, DLCO:carbon monoxide diffusing capacity, FVC: forced vital capacity

Table 2: Baseline characteristics according to diagnostic performance of BAL fluid

	Diagnostic BALF N=131 (51%)	Non-diagnostic BALF N=126 (49%)	P
Age (mean, years)	42±11	42±12	0.878
Female gender	102 (53%)	75 (67%)	0.589
Ever smokers	34 (24%)	31 (27%)	0.615
DLCO	78.9±19.2	78.2±15.9	0.904
FVC %	87.7±14.7	88.3±14.2	0.773
ACE (U/L)	71.2±49.8	60.0±36.3	**0.067**
Ca (mg/dL)	9.7±0.9	9.6±0.5	0.284
Extrapulmonary involvement	**44 (30%)**	21 (19%)	**0.043**

Radiological findings			
BVB presence	70 (48%)	58 (52%)	0.875
Nodul presence	74 (51%)	45 (49%)	0.702
Interseptal lines presence	80 (55%)	50 (45%)	0.071
GGO presence	74 (51%)	45 (49%)	0.234
Pleural thickening	62 (47%)	61 (54%)	0.876
Greatest lymph node diameter	16.3±4.3	17.1±3.9	0.692
Total tomography score	6,3±3,1	6,0±3,1	0,473

ACE: angiotensin converting enzyme, BALF: bronchoalveoler lavage fluid, BVB:bronchovascular bundles, Ca:calcium, DLCO:carbon monoxide diffusing capacity, FVC: forced vital capacity, GGO: ground glass opacity

Table 3: Bronchoalveolar lavage fluid analysis according to smoking status

	Non-smokers	Smokers	P
Lymphocytes (%)	42	39.3	0.353
Neutrophils (%)	16.9	13.7	0.044
Macropahages (%)	40.06	44.9	0.087
Eosinophils (%)	2.57	2.53	0.899
CD4/CD8	5.66	5.68	0.989

Table 4: Bronchoalveolar lavage fluid analysis according to radiographic stages

	Stage 0	Stage 1	Stage 2	Stage 3	P
Lymphocytes (%)	51	41	41.4	34.7	0.419
Neutrophils (%)	14	16.2	17.8	15.9	0.549
Macrophages (%)	31.3	41.2	38.9	52.1	0.051
Eosinophils (%)	3.6	2.4	2.7	2.7	0.437
CD4/CD8	6.4	5.7	5.3	4.5	0.794

Table 5: Bronchoalveolar lavage fluid analysis according to presence of extrapulmonary involvement

	Extrapulmonary involvement absence	Extrapulmonary involvement presence	P
Lymphocytes (%)	41	43	0.342
Neutrophils (%)	17	16	0.431
Macrophages (%)	41	39	0.424
Eosinophils (%)	2.7	2.5	0.794
CD4/CD8	5.05	6.56	0.02

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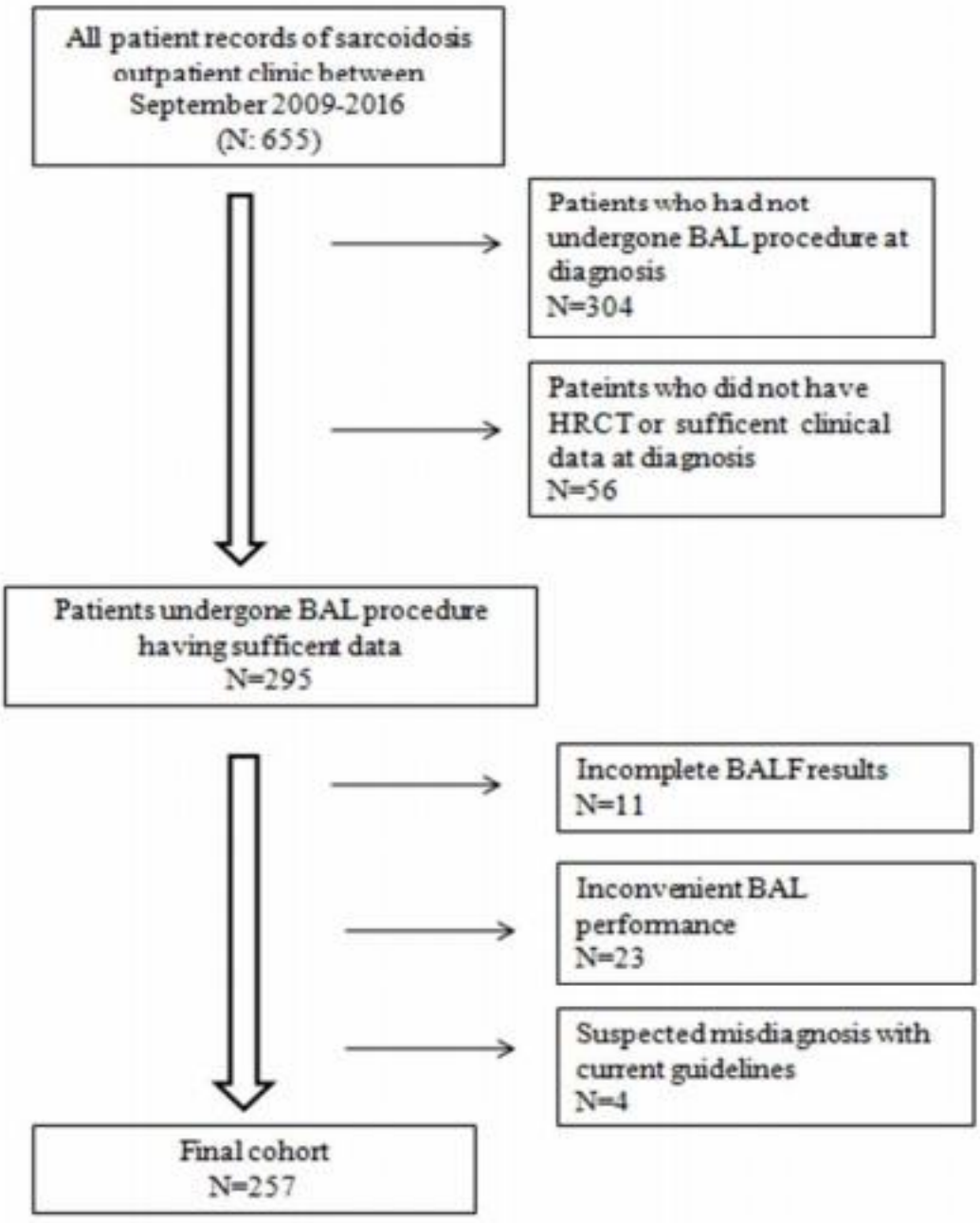

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Figure 1

BAL: bronchoalveolar lavage, BALF: broncholaveolar lavage fluid, HRCT: high-resolution computed tomography

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