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Clinical Features and Prognostic Significance of Endobronchial Sarcoidosis

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Authors' contributions

This work was carried out in collaboration between all authors. Author HY has data responsibility and designed the study. Author CT is responsible for study design and wrote the draft of the manuscript. Author MB is responsible for patient data. Author SD is responsible for patient follow-up. Author AB performed statistical analysis. Author MS is the consultant statistician. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Endobronchial involvement may occur in patients with sarcoidosis. Although the prevalence of bronchial abnormalities is high, there are no firm data establishing the clinical features and prognosis of sarcoidosis in these patients. The aim of our study was to define the clinical characteristics and prognosis of patients with endobronchial sarcoidosis.
Methods: Clinical and laboratory findings of 44 patients with endobronchial sarcoidosis and 46 patients without endobronchial involvement seen at our institution, were evaluated retrospectively. The patients fulfilled clinical, radiologic or both features of sarcoidosis supported by the histopathologic evidence of noncaseating granulomas. Six to ten bronchial biopsies were taken from each patient. The sample was considered positive if it demonstrated noncaseiting granulomas with negative bacterial, fungal and mycobacterial cultures.
Results: Bronchial biopsy was more positive in 84% of the abnormal appearing airways, biopsy provided diagnostic tissue in 32% of the normal appearing mucosa. The most frequent

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bronchoscopic finding was miliary infiltration followed by nodular and erythematous lesions. Serum ACE, serum and urinary Ca levels were higher (51.4±14.3 IU/L vs 37.3±15.1 IU/L, p<0.01; 8.42±3.6 mg/dL vs 10.8±2.9 mg/dL, p<0.01; 244.9±32.4 mg/day vs 379.6±36.8 mg/day, p<0.01) in patients with endobronchial involvement. There was no significant difference between FEV_1, FVC, TLC and $DLCO/V_A$. The extrapulmonary organ involvement (p<0.02) and progressive disease (p<0.03) was more frequent in patients with endobronchial disease.

Conclusion: Endobronchial involvement in sarcoidosis appears to be a significant predictive risk factor for progressive disease. Extrapulmonary organ involvement was also higher in these patients contributing to a worse prognosis.

Keywords: Sarcoidosis; endobronchial sarcoidosis; bronchoscopy; prognosis.

1. INTRODUCTION

Sarcoidosis is a systemic disease of unknown origin that predominantly affects the lungs and the intrathoracic lymph nodes. Nonnecrotizing granulomas are the pathologic hallmark of the disease and usually occur in the bronchial submucosa facilitating bronchoscopic diagnosis by endobronchial lung biopsy [1,2]. The bronchial mucosa in sarcoidosis may appear normal or appears inflamed with miliary or large nodules containing noncaseiting granulomas. Endobronchial disease is common and granulomas are found in the lungs with a positive endobronchial biopsy findings in 40 to 70 percent of the patients [3-6].

Although endobronhial disease is frequent, data concerning the clinical characteristics of these patients is missing. The aim of our study was to investigate the clinical features of endobronchial sarcoidosis. Another objective of our study was to assess the prognostic significance of endobronchial involvement in sarcoidosis. Therefore, we undertook a retrospective study in patients who underwent FOB for suspected sarcoidosis to characterize the clinical aspects and outcome of endobronchial disease.

2. MATERIALS AND METHODS

We retrospectively evaluated ninety sarcoidosis patients attending our center between January 1990 and December 2013. The study has been approved by the IRB/Ethics Committee of Cerrahpasa Medical Faculty and each patient provided informed, written consent. Patients fulfilled the American Thoracic Society/European Respiratory Society criteria of sarcoidosis [1]. All subjects underwent pulmonary function tests, $DLCO/V_A$ (diffusing capacity divided by alveolar ventilation), chest x-ray, thorax computed tomography and FOB (fiberoptic bronchoscopy). The medical charts were used to obtain data about patient age, sex, radiologic stage, laboratory, pulmonary function tests, bronchoscopy and histopathologic findings. Sputum, bronchial lavage or BAL culture were done to exclude infection. Six to ten bronchial biopsies were taken from each patient. In patients with normal-appearing mucosa biopsies were obtained from the main and secondary carenas of both lungs. The patients were classified into two groups according to the presence or absence of endobronchial involvement identified by the histopathologic examination of the bronchial biopsy specimens.

Serum biochemistry consisted of complete blood count, liver function, renal function tests, serum Ca (calcium), urinary Ca, erythrocyte sedimentation rate, C-reactive protein and ACE (angiotensin-converting enzyme). Abnormal liver or renal function tests, high serum ACE, hypercalcemia and hypercalcuria were considered to be present if they were above the normal range. Chest roentgenograms were staged as follows: stage 0: normal, stage 1: bilateral hilar lymphdenopathy, stage 2: bilateral hilar lymphadenopathy and parenchymal involvement, stage 3: parenchymal involvement only and stage 4: pulmonary fibrosis [7]. Spirometry was performed according to the ATS/ERS recommendations. $DLCO/V_A$ was measured with the single-breath technique and was adjusted for alveolar ventilation (V_A). The pulmonary function tests and $DLCO/V_A$ were interpreted in accordance with the guidelines of ATS (8). Values for the pulmonary function tests and $DLCO/V_A$ were considered abnormal if they fell outside the 95% confidence interval for the predicted values. The evidence of restrictive (reduced TLC [total lung capacity] or FVC [forced vital capacity] and normal or high FEV_1/FVC), or decreased diffusion capacity ($DLCO/V_A$< %80) were considered abnormal. For evidence of skin and ocular sarcoidosis all patients were screened by a dermatologist and an opthalmologist.

Central nervous system involvement was considered to exist if neurologic findings were positive, a lesion was confirmed by computed tomography or magnetic resonance imaging and diagnosed by a consultant neurologist.

FOB was performed in the standart fashion under local anesthesia in all patients. Airway appearance was reported as normal or abnormal. Abnormal airways were defined as having erythematous, mucosal thickening, miliary or nodular lesions. In patients with normal appearing mucosa, ten biopsies were taken from the main, secondary carenas and bronchial mucosa. In patients with abnormal mucosa, four to six biopsies were taken from the lesion sites. The biopsy was considered positive if it revealed nonnecrotizing granulomas without mycobacterial or fungal organisms. Bronchial or BAL lavages cultures for bacteria, fungus and mycobacteria were done to exclude infection. In order to determine the presence of endobronchial involvement, only patients with positive histologic bronchoscopic biopsy evidence of sarcoidosis were included in this group. Organ involvement was classified as less than three and three or more organs involved.

Thirty-two patients received corticosteroids, ten patients received azathioprine and six patients received methotrexate. Clinical, laboratory, pulmonary function tests and radiology findings were first evaluated 3 months after diagnosis and every 6 months thereafter. The mean follow-up of the patients was 86.4±25.6 months.

Clinical findings and prognosis of patients with endobronchial involvement were compared to patients without endobronchial disease. The χ^2 test was used for categorical variables as appropriate. Logistic regression was applied to determine the effect of age, gender and endobronchial involvement on prognosis. After checking for normality, Student's t-test was done to compare the difference between serum ACE, serum Ca, urinary Ca, PFTs and DLCO/V_A of the two groups. All tests were two tailed and a p value less than 0.05 was accepted for statistical significance. Analyses were done using software (SPSS 22.0 version).

3. RESULTS

Ninety patients with sarcoidosis were evaluated during the study. Table 1 shows the demographic composition of the entire cohort. Airway appearance was normal in 68 (70.8%) of the patients. Histopathologic examination of the bronchial mucosa biopsy was positive revealing nonnecrotizing granulomatous inflammation in subjects with endobronchial involvement. Noncaseiting granulomas was identified from endobronchial biopsies in 32 percent of patients with normal endobronchial appearences. The most frequent bronchoscopic finding was miliary infiltration followed by nodular and erythematous lesions. Nine patients had erythematous, twelve patients had nodular, eighteen patients had miliary while fourteen had mixed type of lesions. Smear or culture of bronchial or bronchoalveolar lavage was negative for bacteria, mycobacteria and fungus in all patients. Although bronchial biopsy was more positive in 84% of the abnormal appearing airways, biopsy provided diagnostic tissue in 32% of the normal appearing mucosa.

Diagnostic tissue was obtained during FOB in 78%, in 32% with skin biopsy, in 19% via mediastinoscopy and in 12% by various organ biopsies. None of the patients had a complication associated with the biopsy procedures. Clinical characteristics of the patients are shown in Table 1. The mean follow-up of the patients was 86.4±25.6 months. With respect to spirometric measurements, FEV_1 (forced expiratory volume in one second), FVC, TLC and DLCO/V_A were not significantly different between the two groups. Serum ACE, serum and 24 h urinary Ca was higher ($p<0.001$) in patients with endobronchial disease (Table 1).

Organ involvement (three or more) was significantly higher in patients with endobronchial sarcoidosis ($p=0.002$). Association of endobronchial involvement with prognosis and organ involvement is shown in Figs. 1 and 2. Logistic regression analysis revealed a significant severe prognosis for patients with endobronchial involvement that was 4.497 times more worse than the patients without endobronchial lesions ($p=0.03$).

4. DISCUSSION

Sarcoidosis is a systemic granulomatous disease of unknown origin that can affect any organ in the body. The lungs, eyes, skin, liver, and lymphatic systems are the most common sites. The bronchial mucosa is often involved in sarcoidosis, 40% of patients with stage I and approximately 70% of patients with stage II and III have noncaseating granulomas in bronchial

Table 1. Clinical characteristics of the patients

Characteristics	EB (-) (n=46)	EB (+) (n=44)	p value
Demographics			
Age, yr	31.2±5.1	37.2 ±10.6	0.639
Male patients	17	24	0.869
CXR pattern *			
Stage I	14	12	
Stage II	22	24	
Stage III	10	8	
Spirometry			
FEV_1, % predicted	74.2±14.4	76.1±12.6	0.076
FVC, % predicted	80.9±13.2	84.4±14.1	0.072
TLC, % predicted	82.4±18.3	78±19.2	0.09
$DLCO/V_{A,\ \%}$ predicted	86.1±7.87	84.6±9.1	0.08
Laboratory			
Serum Ca, mg/dL	9.29±0.71	10.86±0.84	0.01
Urinary Ca, mg/day	244.9±32.4	319.6±34.8	0.01
Serum ACE, IU/L	37.3±15.1	51.4±14.3	0.01

*Data are presented as mean±SD or %. *Initial radiologic stage of the patient (reference 7). χ^2 test, Student's t-test and logistic regression were used for statistical analysis*

biopsy specimens [2,9,10]. Because of the airway centered granulomas, even with a normal appearing mucosa, sarcoid granulomas are identified by bronchial biopsy in approximately a third of cases, while diagnostic yield rises to 75 percent in the presence of mucosal abnormalities [3,5]. This retrospective study demonstrates that patients with endobronchial involvement may show significant clinical differences from those without bronchial lesions. Extrapulmonary organ involvement, laboratory findings, and the disease prognosis were more severe in patients with endobronchial disease exhibiting distinctive and contrasting features.

Previous studies have primarily investigated the clinical implications and treatment of bronchial stenosis due to endobronchial granulomas. Few studies have emphasized the functional and bronchoscopic features of endobronchial sarcoidosis but they have not reported the clinical and prognostic consequences of superficial bronchial involvement [3,4,6,11]. They included small number of patients with stenotic bronchial lesions. The authors have provided a broad description, evaluation and treatment options for bronchial stenosis or narrowing due to sarcoidosis. In our study, we investigated the clinical features of endobronchial involvement and its correlation with prognosis. Pulmonary function tests and $DLCO/V_A$ were not significantly different between the two groups. Angiotensin-converting enzyme, serum and urinary calcium levels were significantly higher in subjects with endobronchial involvement. The prognosis and extrapulmonary organ involvement were more severe and frequent compared to patients without endobronchial disease.

Along with the above findings, endobronchial sarcoidosis was identified to be a risk factor for progressive and advanced disease. These patients had approximately four times a worse prognosis than patients without endobronchial involvement. The severe prognosis is probably associated with the high granuloma burden caused by the endobronchial lesions. The increased serum ACE, serum and urinary calcium levels also point out to the high granuloma burden in our cases. These findings emphasize the significance of bronchoscopic biopsies in regard to prognosis and progressive disease. Positive endobronchial biopsy may imply a severe and progressive disease. This finding is unique because previous studies have reported that only proximal stenotic bronchial lesions would be an indicator of serious disease by causing severe bronchial stenosis or narrowing [3-5,12,13]. In our study, endobronchial lesions did not lead to stenosis or narrowing and were superficial and erythematous, miliary or nodular.

Advanced pulmonary sarcoidosis develops in 5-6% of all patients and radiologically evident pulmonary fibrosis develops in approximately 10%. No study has compherensively surveyed all potential risk factors for persistent sarcoidosis.

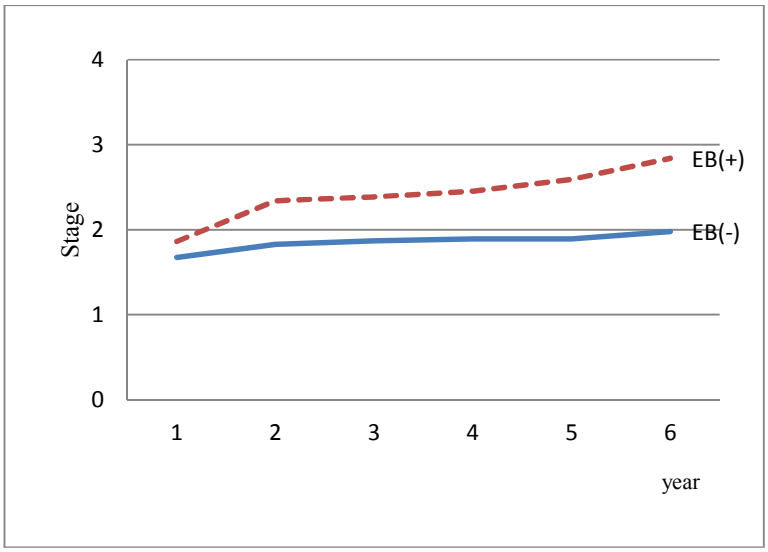

Fig. 1. Disease progression in patients with and without endobronchial involvement. Logistic regression analysis was used statistical evaluation.

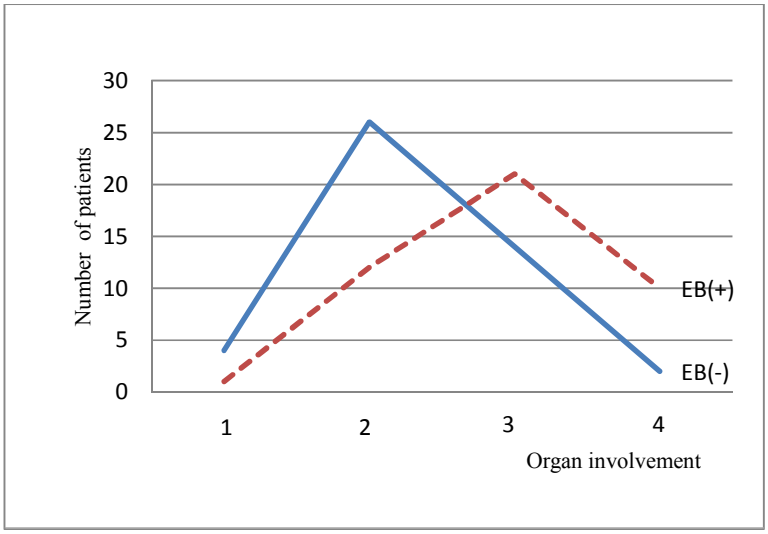

Fig. 2. Organ involvement in patients with and without endobronchial involvement. Logistic regression analysis was used statistical evaluation

While no specific risk factors for advanced pulmonary disease have been identified, numerous factors like old age, lupus pernio, splenomegaly or multiple organ involvement have been defined for progressive and/or advanced disease [14-17]. Our study is exclusive for demonstrating that endobronchial involvement is a significant risk factor for progressive disease. Treatment of sarcoidosis is based on the premise that suppression of granuloma formation results in preservation of organ function and minimization of advanced disease or long-term fibrosis [12,18-20] which may be considered as another supporting evidence for our findings. The prognostic differences between patients may be due to the variable kinetics of granuloma formation in each individual.

We are aware of the limitations of our study. This is a retrospective study with a small sample size. The follow-up interval may be considered short but it is well known that most of the prognostic risk factors for progressive disease become

appearent within two years of diagnosis [14,16,17]. And thirdly, a distinction between localized and diffuse involvement would define the clinical features and prognosis of endobronchial sarcoidosis more precisely. Further prospective and retrospective studies with larger sample sizes are needed to define the clinical and prognostic features of endobronchial sarcoidosis.

5. CONCLUSION

In conclusion, endobronchial involvement appears to be a significant prognostic factor for progressive sarcoidosis. Extrapulmonary organ involvement is also more frequent and severe in these patients. Because bronchoscopic diagnosis of endobronchial lesions is an easy procedure, we recommend that pulmonologists should routinely use bronchoscopy to reveal endobronchial sarcoidosis lesions to identify patients carrying a risk for a worse prognosis. Bronchoscopic biopsy will be useful for the diagnosis of endobronchial involvement even in patients with a normal appearing mucosa thereby necessitating a close follow-up for the early identification of severe disease in such patients without any delay in treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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