Clinical Features and Prognostic Significance of Limited and Diffuse Endobronchial Sarcoidosis

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Authors’ contributions

This work was carried out in collaboration between all authors. Author CT designed the study, wrote the protocol and wrote the first draft of the manuscript. Author HY managed patient data, clinical and laboratory findings. Author MB managed the literature searches. Author SD performed patient follow up. Author AB carried out the statistical analysis, author MS was the consultant statistician and performed data analysis. All authors read and approved the final manuscript.

ABSTRACT

Aims: Airway involvement is a common feature of sarcoidosis and mucosal abnormalities may be evident in the respiratory tract. However, firm data establishing the clinical features and prognosis of sarcoidosis in these patients is lacking although the incidence of endobronchial disease is high. The purpose of this study was to evaluate the clinical features of the patients with limited, diffuse and no endobronchial involvement. Another aim was to investigate the prognostic differences between these patients.

Methods: We conducted a retrospective study to evaluate the clinical and laboratory findings of 48 patients with endobronchial sarcoidosis and 50 patients without endobronchial involvement seen at our institution. The patients fulfilled the 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 noncaseating...
granulomas with negative fungal and mycobacterial cultures. The patients were classified into three groups according to the histopathologic biopsy results: 1) No endobronchial involvement, 2) Limited endobronchial involvement: One biopsy site positive and 3) Diffuse endobronchial involvement: Two or more biopsy sites positive for noncaseating granulomas.

Results: Bronchial biopsy was positive in 82% of the abnormal appearing airways while it was diagnostic in 36% of the normal appearing mucosa. The most frequent bronchoscopic appearance was miliary infiltration. Nodular, erythematous lesions and edematous mucosal swelling were other bronchoscopic findings. There were no significant differences between the three groups for FEV1, FVC, TLC, DLCO/VA serum and 24 h urinary calcium levels. Serum ACE levels were significantly higher (p<0.001) in patients with limited and diffuse bronchial involvement compared to patients with no endobronchial disease. The extrapulmonary organ involvement (p<0.001) and progressive disease incidence was more frequent (p<0.001) in patients with limited and diffuse endobronchial disease.

Conclusions: Endobronchial involvement in sarcoidosis appears to be a significant predictive risk factor for progressive disease. Patients with limited or diffuse endobronchial disease have more severe extrapulmonary organ involvement and a worse prognosis than patients without endobronchial disease. Bronchoscopy may identify such patients carrying a risk factor for progressive sarcoidosis.

Keywords: Sarcoidosis; endobronchial sarcoidosis; prognosis; limited; diffuse.

1. INTRODUCTION

Sarcoidosis is a chronic systemic disease of unknown origin that is characterized by the formation of noncaseating granulomas in the affected organs, predominantly in the lungs and the intrathoracic lymph nodes. 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 noncaseating granulomas. Endobronchial disease is common and granulomas are found anywhere in the respiratory tract with a positive endobronchial biopsy findings in up to 40 to 70 percent of the patients [3-6]. Because of the airway- centered granulomas, even in the normal appearing mucosa sarcoid granulomas are identified by bronchial biopsy in approximately a third of cases, while the diagnostic yield rises up to 75 percent in the presence of mucosal abnormalities [3-5].

Although endobronchial disease is frequent in sarcoidosis, data concerning the clinical characteristics and prognosis of such patients is missing. The aim of our study was to investigate retrospectively the clinical features of limited and diffuse 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 limited and diffuse endobronchial disease.

2. MATERIALS AND METHODS

Ninety-eight sarcoidosis patients attending our center between January 1990 and July 2015 were evaluated retrospectively for endobronchial disease by FOB. The study has been approved by the IRB/Ethics Committee of Cerrahpaşa Medical Faculty and each patient had provided informed, written consent. Patients fulfilled the American Thoracic Society/European Respiratory Society criteria of sarcoidosis [1]. All subjects underwent pulmonary function tests, DLCO/VA, chest x-ray, thorax CT and FOB. Laboratory investigations included complete blood count, liver function, renal function tests, serum Ca, 24 h urinary Ca, erythrocyte sedimentation rate, C-reactive protein and ACE. 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 according to the DeRemee as follows: stage 0: normal, stage 1: bilateral hilar lymphadenopathy, 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/VA was
measured with the single-breath technique and was adjusted for alveolar ventilation. The pulmonary function tests and DLCO/VA were interpreted in accordance with the guidelines of ATS [8]. Values for the pulmonary function tests and DLCO/VA were considered abnormal if they fell outside the 95% confidence interval for the predicted values. The evidence of restrictive (reduced TLC or FVC and normal or high FEV1/FVC), or decreased diffusion capacity (DLCO/VA< %80) were considered abnormal. For evidence of skin and ocular sarcoidosis all patients were screened by a dermatologist and an ophthalmologist. Central nervous system involvement was considered to exist if neurologic findings were positive, a lesion was confirmed by CT or MRI and diagnosed by a consultant neurologist.

Clinical findings and prognosis of patients with limited and diffuse endobronchial involvement were compared to patients without endobronchial disease. The χ2 test was used for categorical variables as appropriate. Logistic regression was applied to determine the effect of age, gender and endobronchial involvement on prognosis. Krukal-Wallis test and Bonferroni corrected two way Mann-Whitney test were used for comparision of the groups. After checking for normality, Anova was done to compare the difference between serum ACE, serum Ca, 24 h urinary Ca, PFTs and DLCO/VA of the three 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-eight patients with sarcoidosis were evaluated during the study. Table 1 shows the demographic composition of the patients. Airway appearance was normal in 64 (64/98, 65.3%) patients. Histopathologic examination of the bronchial mucosa biopsy was positive in 48 subjects (48/98, 48.9%) revealing noncaseiting granulomatous inflammation. Noncaseiting granulomas were identified from endobronchial biopsies in 36 percent of patients with normal endobronchial appearances. The most frequent bronchoscopic finding was miliary infiltration (38%) followed by nodular (18%) and erythematous (16%) lesions while 16 patients (16.3%) had mixed type of lesions. Smear or culture of bronchial lavage was negative for bacteria, mycobacteria and fungus in all of the patients. Although bronchial biopsy was more positive in 82% of the abnormal appearing airways, biopsy provided diagnostic tissue in 36 percent of patients with normal endobronchial appearances. The most frequent bronchoscopic finding was miliary infiltration (38%) followed by nodular (26%) and erythematous (18%) lesions while 16 patients (16.3%) had mixed type of lesions. Smear or culture of bronchial lavage was negative for bacteria, mycobacteria and fungus in all of the patients. Although bronchial biopsy was more positive in 82% of the abnormal appearing airways, biopsy provided diagnostic tissue in 36% of the normal appearing mucosa.
characteristics of the patients are shown in Table 1. Serum ACE was significantly (p<0.001) higher in patients with limited and diffuse endobronchial involvement (Table 1) compared to patients with no endobronchial disease.

Likelihood ratio of organ involvement (three or more) was significantly higher in patients with limited (67%) and diffuse endobronchial disease (75%) compared to patients without endobronchial involvement (58%) (p<0.001). 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 limited endobronchial involvement that was 4.24 times worse than the patients without endobronchial lesions (p<0.001) while the prognosis was 7.32 times worse in patients with diffuse disease (p<0.001).

Table 1. Clinical characteristics of the patients with and without endobronchial involvement in sarcoidosis

| Characteristics     | NEI (n=50) | LEI (n=24) | DEI (n=24) | p value |
|---------------------|------------|------------|------------|---------|
| **Demographics**    |            |            |            |         |
| Age, yr             | 31.2±0.7   | 39.1±2.1   | 36.4±2.3   | 0.32    |
| Male patients       | 18         | 12         |            | 0.19    |
| **Radiologic stage**|            |            |            |         |
| Stage I             | 17         | 7          | 8          |         |
| Stage II            | 21         | 12         | 10         |         |
| Stage III           | 12         | 5          | 6          |         |
| FEV1, % predicted   | 72.6±12.8  | 76.1±12.4  | 74.1±11.2  | 0.26    |
| FVC, % predicted    | 80.2±14.6  | 79.6±9.8   | 82.1±12.6  | 0.49    |
| TLC, % predicted    | 81.2±15.2  | 77.9±13.9  | 79.8±14.3  | 0.28    |
| DLCO/VA, % predicted| 84.3±7.8   | 80.7±6.9   | 82.7±8.6   | 0.34    |
| Serum Ca, mg/dL     | 8.98±0.91  | 9.16±0.62  | 9.12±0.6   | 0.064   |
| Urinary Ca, mg/day  | 256.4±36.6 | 258.2±32.7 | 259.6±34.8 | 0.062   |
| Serum ACE, IU/L     | 36.56±2.4  | 53.56±3.6  | 59.8±4.3   | 0.001   |

Data are presented as mean±SD or %. * Initial radiologic stage of the patients. χ² test, ANOVA, Kruskal-Wallis test and Bonferroni corrected two way Mann-Whitney test were used for statistical analysis. NEI: no endobronchial involvement, LEI: limited endobronchial involvement, DEI: diffuse endobronchial involvement

Fig. 1. Disease progression in patients with and without endobronchial involvement
4. DISCUSSION

The classic anatomic distribution of sarcoidosis is along the bronchovascular bundles and lymphatics [6]. Therefore, 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 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]. Shorr and colleagues have shown that 71% of sarcoidosis patients had bronchial abnormalities and in even in patients with normal appearing airways, granulomas can be identified in 30% of the patients [3]. Our study demonstrated that patients with limited or diffuse endobronchial disease showed significant clinical differences from those without airway involvement. Extrapulmonary organ involvement and the disease prognosis were more severe in patients with endobronchial disease exhibiting distinctive and contrasting features.

Previous studies have only demonstrated the clinical implications and treatment of bronchial stenosis most frequently due to endobronchial granulomas. Few studies have emphasized the functional and bronchoscopic features of endobronchial sarcoidosis, reporting the clinical and prognostic consequences of stenosis due to proximal bronchial involvement in a small number of patients [3,4,6,11]. The authors have provided a broad description, evaluation and treatment options for bronchial stenosis or narrowing of sarcoidosis. In our study, we defined the clinical features of limited and diffuse endobronchial involvement. We also evaluated the difference between prognosis and extrapulmonary organ involvement in patients with and without endobronchial disease. Pulmonary function test, DLCO/VA, serum and urinary calcium levels were not significantly different between the three groups in our study. Angiotensin-converting enzyme, was significantly higher in the LEI and DEI groups than the NEI group.

Limited and diffuse endobronchial sarcoidosis appear to be a significant factor for progressive disease. LEI patients had approximately four times a worse prognosis while the prognosis was approximately seven times worse in the DEI group than the NEI patients. The severe prognosis is probably associated with the high granuloma burden caused by endobronchial lesions. This finding is also supported by the raised levels of serum ACE levels reflecting the high granuloma burden in these two group of patients. Our results emphasize the significance of bronchoscopic biopsies in regard to prognosis and a progressive disease. Positive endobronchial biopsy identifying limited or diffuse type of airway involvement may reveal a severe
and a progressive disease. This finding is unique because previous studies have reported that only proximal stenotic bronchial lesions would be an indicator of serious disease [3-5,12,13]. In our study, endobronchial lesions did not cause stenosis or narrowing but were superficial or nodular. More diffuse the endobronchial involvement with the consequent higher granuloma burden, worse was the prognosis in our patients.

The second aspect of our study was that extrapulmonary organ involvement was more frequent and severe in the LEI and DEI group compared to the NEI patients contributing to the worse prognosis. It is that the higher the granuloma burden, caused by diffuse endobronchial involvement, more severe is the extrapulmonary organ involvement than the other two groups. This is supported by the fact that DEI patients showed the most unfavourable clinical implications compared to LEI and NEI groups. Our results suggest that extrapulmonary organ involvement is also dependent upon the burden of noncaseating granulomas in sarcoidosis.

Persistent or advanced disease develops in 5-6% while radiologically evident pulmonary fibrosis occurs in approximately 10% of all sarcoidosis patients. No study has comprehensively surveyed all potential risk factors for persistent sarcoidosis. 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 especially diffuse endobronchial involvement is a significant risk factor for severe progressive disease and severe extrapulmonary organ involvement. Recently, Yanardag et al. [18] has demonstrated that endobronchial involvement may be a significant risk factor for severe progressive disease, but without a distinction between limited and diffuse endobronchial involvement.

Although sarcoidosis that is progressive or chronic does not always eventuate in fibrotic disease, presence of endobronchial involvement identified by bronchoscopy may be a significant marker for severe prognosis. Apart from diagnosis of the disease, FOB should be performed in every sarcoidosis patient for the identification of severe prognosis with multiple biopsies taken from different sites. 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 [12,19-21] 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. Further prospective studies including more bronchoscopy biopsy samples may define the limited and diffuse endobronchial sarcoidosis more precisely thereby enlightening the clinical features and the prognosis of these patients. The follow-up interval may be considered short but it is well known that most of the prognostic risk factors for progressive disease become apparent within two years of diagnosis [14,16,17], which was approximately eight years in our patients. And thirdly, although the bronchoscopists were very experienced, the biopsy samples may be inadequate, may not represent the disease site or may not be deep enough for the identification of noncaseating granulomas, especially in the normal appearing mucosa.

In conclusion, endobronchial involvement, whether limited or diffuse, appears to be a significant prognostic factor for progressive disease in sarcoidosis. Because bronchoscopic diagnosis of endobronchial lesions is an easy procedure, we recommend that pulmonologists should routinely use bronchoscopy and obtain multiple mucosal biopsies to identify endobronchial sarcoidosis for establishing patients carrying a risk for a worse prognosis. Another important aspect of our study is that endobronchial disease also appears to be a significant factor for severe organ involvement in sarcoidosis. Bronchoscopy will thereby be useful for the diagnosis of endobronchial involvement thereby necessitating a close follow-up for the early identification of progressive disease in such patients without any delay in treatment.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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