

# Clinical features and prognostic significance of splenic involvement in sarcoidosis

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## Abstract

Sarcoidosis is a systemic disease characterized by noncasefied granulomas in various organs. Incidence of splenic disease is variable and is reported to occur in 6.7 to 77 percent of the patients. Firm data establishing the clinical features and the association of splenic involvement with prognosis in sarcoidosis is scant. The aim of our study was to investigate the clinical features and the consequence of splenic involvement on the prognostic outcome of sarcoidosis patients.

We evaluated the clinical and laboratory findings in 82 sarcoidosis patients. Forty-two patients with splenic involvement were compared to forty sarcoidosis patients without splenic disease in regard to laboratory findings, endobronchial disease, extrapulmonary organ involvement, and prognosis. Lung biopsy sample was considered positive if it demonstrated noncaseating granulomas with negative fungal and mycobacterial cultures. Splenic sarcoidosis was identified by ultrasound or computed tomography and was designated as limited, diffuse or without splenic involvement. Extrapulmonary organ sarcoidosis was classified as extensive and limited. Endobronchial disease was categorized as limited or diffuse involvement.

The most commonly comprised organ was lung in 95% of the cases followed by lymph nodes, skin, eye, spleen and liver in the order of frequency. Splenic disease was diffuse in 22 patients. Of these patients,

14 had extensive extrapulmonary organ involvement while 16 had diffuse endobronchial disease. There was no significant difference between the three groups for FEV<sub>1</sub>, FVC, TLC, DLCO/V<sub>A</sub>, serum and 24h urinary calcium levels. Serum ACE was higher in patients with diffuse splenic involvement (p<0.001). Incidence of persistent chronic disease was significantly higher (p<0.001) in patients with diffuse splenic sarcoidosis. Extensive extrapulmonary organ involvement and diffuse endobronchial disease were more common (p<0.001) in this group.

Extensive extrapulmonary organ involvement and diffuse endobronchial disease were more frequent in patients with diffuse splenic sarcoidosis. Patients with diffuse splenic granulomas had a worse prognosis than the patients without splenic involvement or patients with limited splenic disease. Diffuse splenic involvement emerges to be a significant risk factor for persistent chronic sarcoidosis. Extensive granuloma burden in an organ may be the decisive clinical marker for the prognostic outcome of sarcoidosis patients.

## Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown origin that is characterized by the formation of noncaseous granulomas in the affected organs, predominantly in the lungs and the intrathoracic lymph nodes [1-3]. Despite the fact that the noncasefied granulomas most often appear in the lungs and lymph nodes, virtually any organ can be affected. Incidence of splenic involvement from sarcoidosis has been reported to occur between 6.7% and 77% of the patients. The distinctly high variable frequency of splenic involvement depends on whether it is detected by physical examination, radiologic imaging, or [4-7] a tissue biopsy. The silent clinical profile and the lack of specific laboratory findings that indicate splenic sarcoidosis may be crucial in the highly variable incidence. Although splenic disease is a prominent feature of sarcoidosis, data relevant to the clinical aspects of splenic involvement and the consequence of spleen sarcoidosis on the prognostic outcome of these patients is scant.

This retrospective study was designed to delineate the clinical and prognostic features of splenic involvement in sarcoidosis patients. Another objective of our study was to assess the significance of splenic involvement in regard to extrapulmonary organ disease and endobronchial involvement.

## Materials and Methods

Seventy-four sarcoidosis patients attending our center between February 1990 and June 2017 were evaluated retrospectively for splenic involvement from sarcoidosis. The study has been approved by the IRB/Ethics Committee of Cerrahpasa Medical Faculty (01/11/2015, 381632) Each patient had provided informed and written consent. Pa-

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Key words: Sarcoidosis; spleen; prognosis; endobronchial sarcoidosis; extrapulmonary organ involvement.

Contributions: CT, study design, manuscript writing; HY, patient data and evaluation; MP, contribution to patient follow-up and manuscript references; MB, statistical analysis processing.

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tients fulfilled the American Thoracic Society/European Respiratory Society criteria of sarcoidosis [1]. All subjects underwent pulmonary function tests,  $DLCO/V_A$  [Carbon monoxide diffusion capacity of the lung corrected for alveolar volume ( $DLCO/V_A$ )], chest x-ray, abdominal ultrasound, FOB [Fiberoptic Bronchoscopy (FOB)], thorax and abdominal CT [Computed Tomography (CT)]. The patients were classified into three groups as WSI [Without Splenic Involvement (WSI)], LSI [Limited Splenic Involvement (LSI)], and DSI [Diffuse Splenic Involvement (DSI)]. Forty-two patients with splenic sarcoidosis were compared to forty patients without splenic involvement in regard to clinical findings, disease prognosis, extrapulmonary organ, and endobronchial involvement.

Laboratory investigations included complete blood count, liver function, renal function tests, serum Ca, 24h urinary Ca, erythrocyte sedimentation rate, C-reactive protein and ACE [Angiotensin-Converting Enzyme (ACE)]. Abnormal liver or renal function tests, high serum ACE, hypercalcemia and hypercalcuria were determined to be present if they were above the normal laboratory range. The DeRemee criteria; 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 [8] were used to evaluate the chest roentgenograms. Splenic sarcoidosis was identified by ultrasound and CT. Disease involvement was diagnosed by needle aspiration in two patients and splenectomy material in one patient.

The pulmonary function tests and  $DLCO/V_A$  were performed according to the ATS/ERS recommendations. The results interpreted in accordance with the ATS guidelines [9].  $DLCO/V_A$  was measured with the single-breath technique that was adjusted for alveolar ventilation. Values for the pulmonary function tests and  $DLCO/V_A$  were evaluated as abnormal if they were outside the 95% confidence interval of the predicted values. The evidence of restrictive disease was revealed by a reduced TLC [Total Lung Capacity (TLC)] or FVC [Forced Vital Capacity (FVC)] and a normal or a high  $FEV_1/FVC$  [Forced Expiratory Volume in one second to Forced Vital Capacity ratio ( $FEV_1/FVC$ )]. A decreased diffusion capacity indicated by a  $DLCO/V_A < 80\%$  value was denoted as abnormal. All patients were screened by a dermatologist and an ophthalmologist for the evaluation of cutaneous and ocular sarcoidosis. Central nervous system sarcoidosis was determined to exist if neurologic examination was positive, a lesion was identified by CT [Computed Tomography (CT)] or MRI (Magnetic Resonance Imaging (MRI)), and diagnosed by a consultant neurologist.

Epidemiological, clinical, and histopathologic findings were obtained from the medical records of the patients. Bronchoscopy was done under local anesthesia. Six bronchial biopsies were taken from each patient with an abnormal mucosa. In patients with a normal mucosal appearance eight biopsies from different sites and main carenas of both lungs were taken. Splenic sarcoidosis was classified as LSI in the presence of two granulomas and as DSI if more than two granulomas were present that were identified by ultrasound or CT imaging. If radiologic imaging of the spleen were normal, the patients were classified as WSI. Extrapulmonary organ involvement was classified into two groups as LOI [Limited Extrapulmonary Organ Involvement (LOI)] if less than three organs were involved and as EEI [Extensive Extrapulmonary Organ Involvement (EOI)] when three or more organs were involved. Endobronchial disease was denoted as LEI [Limited Endobronchial Involvement (LEI)] in the presence of one positive bronchial biopsy sample and as DEI [Diffuse Endobronchial Involvement (DEI)] if two or more samples were positive for noncasefied granulomatous inflammation. Sarcoidosis activity was evaluated in regard to progressive stage, deterioration of pulmonary function tests, permanent decline of  $DLCO/V_A$  values, extrapulmonary organ involvement, and the presence of severe systemic symptoms.

Twenty patients were treated with corticosteroids, eight patients received azathioprine and four patients were commenced on methotrexate. Clinical, laboratory, pulmonary function tests, and radiology findings were evaluated every 3 months after diagnosis. Laboratory survey during the follow-up period included blood count, serum biochemistry, serum and 24h urinary calcium. Lung function tests  $FEV_1$ , FVC, TLC, and  $DLCO/V_A$  were done while ABG analysis was performed when requisite. The outpatient control was scheduled every 3 to 6 months according to the clinical profile of the patient. The mean follow-up period was  $96.4 \pm 16.8$  months. Progressive persistent disease was defined as worsening pulmonary or systemic symptoms, severe pulmonary function impairment, extrapulmonary organ involvement and evidence of significant worsening of radiologic findings. As sarcoidosis often resolves within two to five years after diagnosis [10-12] patients who had manifestations of persistent disease five years following diagnosis were classified as chronic persistent disease. Since persistence of active inflammation more than two years from diagnosis reduces the chance of resolution substantially [3,11] patients who showed a benign course with negligible symptoms or trivial laboratory findings after three years from diagnosis were delineated have a stable disease.

Scale variables were represented by mean  $\pm$  standard deviation. Patients were classified into three groups as without splenic involvement, and with limited, or diffuse splenic involvement. Clinical findings, prognosis, and endobronchial involvement were compared between the three groups. Statistical differences between patients without splenic disease, with limited, and diffuse disease were evaluated in regard to prognosis, limited or extensive extrapulmonary organ sarcoidosis, and limited or diffuse endobronchial involvement. The  $\chi^2$  test was used for categorical variables as appropriate. Logistic regression was applied to determine the effect of age, gender and splenic disease on prognosis. Kruskal-Wallis test and Bonferroni corrected two way Mann-Whitney test were used for comparison of the groups. After checking for normality, Anova was done to compare the differences between serum ACE, serum Ca, 24h urinary Ca, PFTs and  $DLCO/V_A$  of the three groups. Statistical analyses were evaluated using software (SPSS 22.0 version). All tests were two tailed and a threshold p-value less than 0.05 was accepted for statistical significance.

## Results

Eighty-two sarcoidosis patients participated in the study. Demographic composition, radiologic stage, laboratory and pulmonary function test results of the patients are shown in Table 1. Tuberculin test was negative in 68 (82%) patients. Bronchoscopic examination of the airways revealed mucosal abnormalities in 54 (65.8%) patients. The most frequent bronchoscopic finding was miliary infiltration (34%) followed by nodular (28%) and erythematous (24%) lesions while 19 patients (23.1%) had mixed type of lesions. Histopathologic evaluation of the bronchial mucosa biopsy was positive in sixty-two subjects (75.6%) revealing noncasefied granulomatous inflammation. Noncasefied granulomas were identified from the endobronchial biopsy samples in 26 (32.2%) of the patients with a normal mucosal appearance. Culture of bronchial lavage was negative for bacteria, mycobacteria and fungus.

Diagnostic histopathologic tissue was obtained by FOB in 76%, by skin biopsy in 36%, via mediastinoscopy in 12% and by various organ biopsies in 28% of the patients. None of the subjects had a complication associated with the biopsy procedures. There was no significant difference between the  $FEV_1$ , FVC, and TLC values of the three groups while  $DLCO/V_A$  was lower ( $p < 0.01$ ) in patients with diffuse splenic in-

involvement. Of the forty-two patients with splenic sarcoidosis, 22 had diffuse splenic involvement. Logistic regression with Kruskal-Wallis test and Bonferroni corrected two way Mann-Whitney test revealed no statistical difference of age and gender on prognosis. Blood biochemistry, serum and 24 h urinary Ca values were not distinct ( $p < 0.094$ ,  $p < 0.12$ ) (Table 1) between the groups. Serum ACE was higher in patients with diffuse splenic disease ( $p < 0.01$ ). Association of splenic disease with prognosis, extrapulmonary organ, and endobronchial involvement is shown in Figures 1, 2, and 3. Likelihood ratio of extensive extrapulmonary organ involvement was higher in patients with diffuse splenic sarcoidosis compared to patients without splenic disease ( $p < 0.001$ ) or to patients with limited splenic involvement.

Diffuse endobronchial involvement (52.7%) was significantly ( $p < 0.001$ ) more frequent in patients with diffuse splenic disease. Patients with diffuse splenic involvement had the most severe prognostic outcome among the three groups. Logistic regression analysis revealed a 1.6 times worse prognosis, a 1.4 times more frequent extensive extrapulmonary organ disease, and a 1.3 times more common diffuse endobronchial involvement ( $p < 0.001$ ) in patients with diffuse splenic sarcoidosis compared to patients without splenic disease. Incidence of persistent chronic sarcoidosis was significantly higher in patients with diffuse splenic involvement ( $p < 0.01$ ) than patients without splenic disease. Diffuse endobronchial disease was more common ( $p < 0.01$ ) in this group.

## Discussion

Splenic involvement is variable and occurs in 6.7 to 77 % of the sarcoidosis patients [4-7]. Autopsy reports reveal higher incidences as 38-77% while the incidence is between 24-59 % with fine needle aspiration [5,6,10]. Clinically overt organ enlargement is detected in less than 14% and 60% of these are asymptomatic [11,12]. Currently, data relevant to prognosis in sarcoidosis patients with splenic disease is

scarce because the silent clinical course is silent and the incidence is variable [11-13]. Lack of specific or diagnostic laboratory findings that indicate spleen involvement may also have contributed to the low variable incidence of splenic disease in these studies [13-15]. Our results imply that diffuse spleen involvement is a significant risk factor for a severe prognostic outcome in sarcoidosis. The second crucial conclusion is the frequent occurrence of extensive extrapulmonary organ involvement in patients with diffuse splenic sarcoidosis. Another noteworthy issue of this study is the common presence of widespread endobronchial granulomas in such patients. Existence of a high granuloma burden in the spleen emerges as a crucial clinical indicator of chronic persistent sarcoidosis.

Progressive or chronic sarcoidosis does not always eventuate in fibrotic disease. The main point in the follow-up and treatment of sarcoidosis is the identification of patients carrying a risk factor for a poor outcome or a severe prognosis. In this regard, our study indicates that presence of diffuse splenic involvement appears to be a relevant clinical marker for a severe prognosis. It is well known that the granuloma burden in sarcoidosis is the hallmark of persistent and progressive disease [16]. The adverse outcome in patients associated with diffuse splenic involvement is primarily due to the high granuloma burden. Serum ACE is produced in the epithelioid cells of the sarcoid granuloma and reflects the total granuloma burden in sarcoidosis [3,10,11]. The excessive granuloma load of diffuse splenic disease in our study is justified by the presence of significantly high levels of ACE in these patients. Target strategy in the treatment of sarcoidosis depends on the premise of granuloma suppression, stabilization of organ function, and prevention or minimization of fibrosis [10,16]. The kinetics of granuloma formation and the dynamics of different organ involvement is variable between individual patients as well as in the same patient. The prognostic differences between patients is probably due to the unstable tendency of granuloma formation and distribution in sarcoidosis patients. Our study denotes that the higher the granuloma burden in the spleen of a sarcoidosis patient the worse is the prognosis.

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

Characteristics	WSI (n:40)	LSI (n:20)	DSI (n:22)	p-value
<b>Demographics</b>				
Age (years)	30.4±4.7	32.6±6.2	29.4±5.3	0.28
Male patients	14	9	10	0.16
Female patients	18	11	12	0.14
<b>Radiologic stage*</b>				
Stage I	24	8	5	
Stage II	17	7	8	
Stage III	6	4	5	
Stage IV	1	1	4	
<b>Spirometry</b>				
FEV <sub>1</sub> , % predicted	72.6±12.8	76.1±12.4	74.1±11.2	0.24
FVC, % predicted	80.2±14.6	79.6±9.8	82.1±12.6	0.32
TLC, % predicted	81.2±15.2	77.9±13.9	79.8±14.3	0.18
DLCO/V <sub>A</sub> , % predicted	84.3±7.81	80.7±6.9	82.7±8.6	0.22
<b>Laboratory</b>				
Serum Ca, mg/dL	8.98±0.91	9.16±0.62	9.12±0.68	0.094
Urinary Ca, mg/day	256.4±36.6	258.2±32.7	259.6±34.8	0.12
Serum ACE, IU/L	34.8±6.2	63.7±5.8	79.8±8.4	0.001

\*Initial radiologic stage of the patients.  $\chi^2$  test, ANOVA, Kruskal-Wallis test and Bonferroni corrected two way Mann-Whitney test were used for statistical analysis. WSI, without splenic involvement; LSI, limited splenic involvement; DSI, diffuse splenic involvement. Data are presented as mean±SD or %.

Advanced disease usually develops in no more than 5-6% of all sarcoidosis patients [17,18]. Most of the established prognostic indicators become apparent within two years of disease onset [19,20]. A number of clinical markers have been used up to now to determine the prognosis in sarcoidosis patients with variable achievement [21]. Currently, there are no accurate or absolute specific risk factors for advanced sarcoidosis. Although old age, lupus pernio, splenomegaly, chronic hypercalciuria, multiple organ involvement ( $\geq 3$  organs), absence of lymphadenopathy, ascending radiologic stage, and architectural distortion of the airways or cystic changes have all been defined as potential risk factors for progressive and advanced disease, the statistical significance is not high with a low sensitivity and specificity [19,20,22,23]. Whether all these factors or conditions effect the prognosis of sarcoidosis leading to a persistent chronic disease is not definite. In contrast to previous data, our study is unique to demonstrate that diffuse splenic involvement is associated with a more severe prognosis, more frequent extensive extrapulmonary, and diffuse endobronchial involvement. The primary source of the granulomas, whether the lung or an extrapulmonary organ, effecting the prognosis may not be definitive. The granuloma burden determining the prognostic outcome in our patients is strongly presumptive to be the spleen since the incidence of persistent disease was significantly higher in the diffuse splenic involvement group than the other two groups. Our results reveal that the primary organ predicting the prognostic outcome for sarcoidosis appears to be the site with the redundant granuloma load. Diffuse splenic disease was associated with chronic persistent disease, severe extrapulmonary organ, and diffuse endobronchial involvement thereby leading to a worse prognosis in regard to patients with limited or without splenic disease as stated by

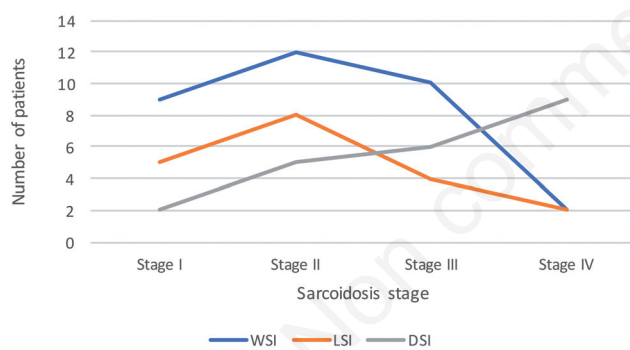


Figure 1. Splenic sarcoidosis and prognosis.

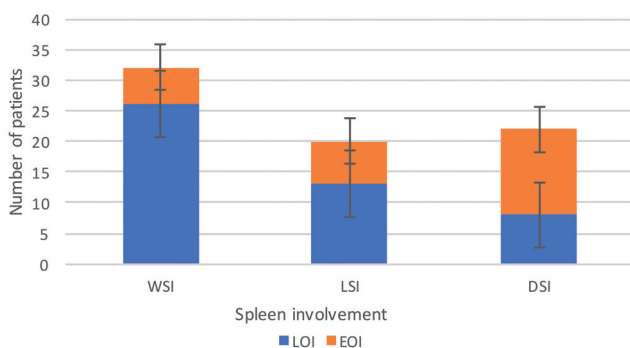


Figure 2. Splenic sarcoidosis and extrapulmonary organ involvement.

Yanardag *et al.* for diffuse hepatic involvement [24]. Furthermore, the presence of widespread granulomas in the spleen also appears to be a useful treatment implication for patients that carry an equivocal treatment criteria in clinical practice.

There are some potential limitations of our study. The first limitation is the small sample size. Second, microgranulomas of the spleen may not be identified by ultrasound and CT imaging and can only be diagnosed by histopathologic evaluation of the spleen. Thirdly, estimation of the accurate granuloma burden in any organ is not possible with the current methods and thereby a more accurate scoring system with a decisive format would be more useful for an objective assessment of the splenic granuloma burden. Fourth, 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 [11,20,22,23] and patients with persistent disease after five years from diagnosis are classified as chronic disease. The mean follow-up period was approximately eight years in our patients. Fifth, the bronchoscopic biopsy samples may not be deep enough for the identification of the noncasefied granulomas, especially in the normal mucosa. Clinical presentation and outcome of sarcoidosis patients show a considerable variation due to the different genetic, hormonal, and environmental aspects for each individual. These factors may play a crucial role on the outcome of sarcoidosis patients. Our patient group consisted of only Caucasian people. It is well-known that sarcoidosis shows a great variability in clinical manifestations and prognostic outcome in regard to genetic background [1,2,25]. We did not investigate racial, genetic and environmental factors in our study. Further studies with larger sample sizes including more heterogeneous patient populations are needed to define the precise association of splenic sarcoidosis with prognosis.

The results of our study suggest that the extensive presence of granulomas in the spleen may be a reliable clinical indicator for chronic persistent sarcoidosis. Diffuse splenic involvement is a decisive prognostic risk factor for progressive disease. Extensive organ involvement and diffuse endobronchial disease are more common in these patients. The incidence of splenic involvement from sarcoidosis is highly variable while most patients are asymptomatic and the incidence of clinically detectable of splenic disease is low. The accurate distinction between persistent chronic and self-limited benign sarcoidosis may cause difficulties in clinical practice. Although progressive sarcoidosis does not always lead to advanced or fibrotic disease, establishing such phenotypes appears to be the pivotal step for management. Diagnosis of disseminated granulomatous splenic involvement by US or CT is a useful, simple, and a noninvasive clinical tool to predict a chronic disease course. Optimal management of sarcoidosis depends upon the

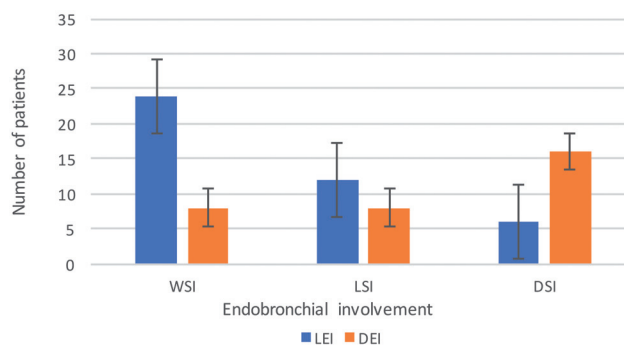


Figure 3. Splenic sarcoidosis and endobronchial involvement.



distinctiveness and lucidity of the treatment goals. Identification of the splenic granuloma load appears to be a prognostic facility for chronic persistent sarcoidosis. This preliminary application may be a practical clinical enterprise for a meticulous follow-up and to determine the treatment options in such patients.

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