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Research Article

Ocular and Lacrimal Gland Involvement in Sarcoidosis Patients

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Abstract

Ocular involvement in sarcoidosis patients is relatively common that may present as the initial manifestation of sarcoidosis. We have retrospectively evaluated the dermographic and clinical, laboratory, and the radiologic manifestations of ocular sarcoidosis with and without lacrimal gland involvement to sarcoidosis patients without eye disease. Another aim was to determine the influence of simultaneous ocular and lacrimal sarcoidosis on the prognosis in sarcoidosis patients.

The patients were assessed for clinical features and prognosis between the three groups including patients without ocular disease, ocular sarcoidosis disease, simultaneous ocular and lacrimal gland involvement in sarcoidosis. Among the 196 patients, 64 (32.6%) had ocular sarcoidosis while lacrimal gland involvement was identified in 32 (16.3%) patients. Concurrent ocular and lacrimal gland sarcoidosis was diagnosed in 18 (9.2%) individuals. Opthalmologic disease was the initial complaint in 16 subjects (8.2%) while asymptomatic ocular sarcoidosis was observed in 14 patients (7.1%) at admission. Red eye appeared as the most frequent symptom occuring in 26 (13.2%) while anterior uveitis was the most commonly involved site in 32 (16.3%) of the patients. The other ocular structures were posterior uvea, papilla, and the sclera in regard to decreasing involvement incidence.

Our findings establish that the concurrent existence of ocular and lacrimal gland involvement in sarcoidosis appears to be an almost unequivocal clinical marker for determining the prognosis in these patients. Lacrimal gland sarcoidosis without ocular involvement was mostly observed at the initial stages of the disease and was found to be a benign marker for sarcoidosis prognosis. In patients with simultaneous eye and lacrimal gland involvement, the clinical, laboratory and the radiological findings displayed a worse profile. Extrapulmonary organ involvement was more frequent while the prognosis revealed a significantly more severe outcome in this group. Ocular sarcoidosis along with synchronous lacrimal gland involvement occurs to be a pernicious presage for a severe, protracted, and chronic sarcoidosis prognosis.

Keywords: *Sarcoidosis; Ocular Sarcoidosis; Lacrimal Gland Sarcoidosis; Prognosis*

Introduction

Ocular involvement in sarcoidosis ranges from 12% - 76% while it may emerge as the presenting or the initial manifestation in approximately 30 - 40% of the patients [1-3]. Ocular sarcoidosis may emerge in any sarcoidosis stage that may involve any part of the ocular compartment [3-5] while most commonly uveitis and conjunctival nodules are detected in these patients [2,4,6]. Involvement of ocular structures due to sarcoidosis may be as high as 79% in systemic sarcoidosis [5,6]. Lacrimal gland is the most frequent site involved in sarcoidosis, with a reported prevalence of 42 - 63% in studies of orbital and ocular adnexal disease and with a 7 - 16% prevalance in patients with systemic disease [7-9]. Sarcoidosis may involve only one organ, display a self-limiting and a benign prognosis without involvement of other tissues that does not lead to any dysfunction. On the other hand, sarcoidosis may involve many sites, mainly the lungs that may lead to a severe disease course resulting in a chronic and protracted profile with severe function loss of the involved organs.

Although many different clinical, laboratory and radiological markers have been proposed to determine the prognosis of sarcoidosis, all of them have been far from providing precise or accurate results for the assessment of prognosis in sarcoidosis patients.

Aim of the Study

Our aim was to investigate the clinical features of simultaneous ocular and lacrimal gland involvement in sarcoidosis compared to patients with and without ocular sarcoidosis. Another target was to assess the influence of coexistent ocular and lacrimal gland involvement on the prognostic outcome of sarcoidosis.

Materials and Methods

This is a retrospective research study including 196 sarcoidosis patients that were evaluated between January 1988 and October 2021 at the Internal Medicine Department of Cerrahpasa Medical Faculty. The survey is an ongoing study of the research initiated by Yanardag., *et al*. [10] previously. All patients conformed to the American Thoracic Society/European Respiratory Society criteria for sarcoidosis diagnosis [11,12]. Laboratory examination consisted of complete blood count, liver and renal function tests, serum Ca, 24h urinary Ca, erythrocyte sedimentation rate, C-reactive protein and serum ACE. Any abnormal or pathologic laboratory finding was accepted to be present if the results were above the normal range. In all patients pulmonary function tests, DLCO/VA (Carbon monoxide diffusion capacity of the lung corrected for alveolar volume), chest x-ray, abdominal ultrasound, FOB (Fiberoptic Bronchoscopy), thorax CT (Computed Tomography), slit lamp biomicroscopy, and fundus examination were done. For chest x-ray evaluation DeRemee criteria were used that reveal; 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 [13]. Chest CT was performed at admission and during the outpatient controls if indicated.

Pulmonary function tests and DLCO/VA were done and assessed according to the ATS/ERS criteria while the obtained results were interpreted in accordance with the ATS guidelines [14,15]. For DLCO/VA measurement the single-breath technique adjusted for alveolar ventilation was used. Pulmonary function test and DLCO/VA values were intrepreted as abnormal if they were outside confidence interval of the predicted values. A reduced TLC (Total Lung Capacity) or FVC (Forced Vital Capacity) with a normal or a high FEV1/FVC (Forced Expiratory Volume in one second to Forced Vital Capacity) ratio indicated a restrictive abnormality. A diffusion capacity revealed by a DLCO/VA value less than 80% value was assessed as abnormal. The patients had a dermatology, neurology, and an opthalmology consultation for the assessment of systemic involvement whenever indicated. Central nervous system involvement was diagnosed if neurologic examination was positive by a consultant neurologist or a relevant lesion was identified by CT or MRI.

Ocular compartment tissue biopsies including the conjuntiva, lacrimal gland, or other structures were done from the involved lesions for diagnosis. Ocular sarcoidosis disease was diagnosed by opthalmological examination or by the existence of non-casefied granulomatous inflammation verified by the histopathologic examination of the biopsy samples. The international ocular sarcoidosis diagnostic criteria were utilized to identify eye involvement [16] including the presence of granulomatous precipitates, iris or, trabecular nodules, lesions of vitrea, multiple chorioretinal peripheral lesions, phlebitis, retinal aneurysm in an inflamed eye, nodules in the optic disc, presence of choroidal nodules, along with bilateral involvement. Conjunctival biopsy was done in the presence of nodules or follicles and randomly in patients without lesions. Lacrimal gland biopsy was performed in patients with a suspicious sarcoidosis involvement.

The sarcoidos patients were classified into three different goups for assessment. Group I included saroidosis patients without ocular involvement. Group II comprised patients with ocular sarcoidosis while group III consisted of patients with simulataneous ocular and lacrimal gland involvement. Data variables of the patients were designated as mean ± standard deviation. Statistical differences between the three groups were compared in regard to prognosis. Chi-square test was used for categorical variables. Logistic regression was used to assess the influence of age and gender on sarcoidosis prognosis. For comparision of the three groups Kruskal-Wallis test and Bonferronni corrected two way Mann-Whitney tests were utilized. To determine the differences between serum ACE, serum Ca, 24h urinary Ca values, PFT and DLCO/Va percentages (actual/predicted) between the three groups analysis of variance was performed. A p value less than 0.05 was accepted as statistically significant. A correlation coefficient r of 0.50 was designated as moderate, r of 0.70 strong and r of 1.0 value revealed perfect correlation. Sarcoidosis activity for persistent chronic disease along with prognosis was determined by analysis of systemic symptom severity, pulmonary function status, perpetual decrease in DLCO/VA values, and progression of radiologic findings.

Seventy six patients were treated with corticosteroids, eighten patients received azathioprine, eighteen patients were commenced on methotrexate and twenty four patients were given both steroids and azathioprine or methotrexate. During the follow-up period the laboratory investigations included blood count, serum biochemistry, ACE, serum and 24h urinary calcium. Pulmonary function tests including FEV_1, FVC, TLC, and DLCO/VA were performed routinely every six months or in case of detoriation. Arterial blood gas analysis was done in patients with symptomatic complaints. Radiologic assessment consisting of chest x-ray, CT and MRI were performed for pulmonary or extrapulmonary organ involvement appraisement. All patients were scheduled to be evaluated at the the outpatient clinic for every three to six months depending on the disease severity and in case of new complaints or symptoms.

Results

Study population consisted of 196 sarcoidosis patients (124 females, 63.2%) with a mean age of 36.8 ± 14.6 years. Group I consisted of 102 (52.0%) sarcoidosis patients without ocular or lacrimal gland involvement, group II included 64 patients with ocular sarcodosis while group III comprised 32 (16.3%) patients with lacrimal disease of whom 18 (9.2%) had simultaneous ocular sarcoidosis. Table 1 depicts the dermographic features and the clinical findings of the patients. Tuberculine test revealed negative results in 76% of the patients. Mucosal abnormalities associated with granulomatous inflammation was found in 36% of the cases during bronchoscopy. Miliary nodules was the most frequent lesion observed in 28% of the patients, followed by nodular (24%), and erythematous lesions (20%) while 14% had a combination of lesions. Granulomatous inflammation was identified from the endobronchial biopsy samples in 128 patients (128/196, 65.3%) while pathologic examination revealed granulomatous inflammation in 48 (48/196, 24.4%) patients with a normal bronchial mucosa. Smear and culture for bacteria, mycobacteria, and fungus obtained by bronchial or BAL did not reveal any organisms in all of the patients.

	Group I	Group II	Group III	r	p
Total # of patients	102	64	32		
Radiology					
Stage 0	32	19	10	0.2	< 0.05
Stage I	38	23	7	0.4	< 0.05
Stage II	24	18	6	0.7	< 0.05
Stage III	6	2	4	0.9	< 0.05
Stage IV	2	2	5	0.8	< 0.01
PFT					
FEV_1 (% predicted)	72.1 ± 14.8	76.4 ± 18.2	74.8 ± 16.4	0.2	< 0.16
FVC (%, predicted)	78.4 ± 16.2	72.6 ± 14.6	76.8 ± 18.4	0.1	< 0.24
TLC (% predicted)	80.2 ± 18.6	82.6 ± 12.8	82.4 ± 16.2	0.1	< 0.12
DLCO/VA (% predicted)	81.4 ± 14.2	80.6 ± 16.4	78.8 ± 14.8	0.1	< 0.18
Laboratory					
Serum Ca (mg/dL)	9.64 ± 4.8	9.48 ± 4.6	10.2 ± 6.4	0.3	< 0.05
Urinary Ca (mg/day)	286.8 ± 20.4	284.6 ± 18.2	290.4 ± 16.8	0.2	< 0.05
Serum ACE (IU/L)	42.6±14.8	54.8±16.4	62.4±18.6	0.2	<0.05

Table 1: *Clinical and radiologic features of the patients.*

Data are presented as mean ± SD or %.

Diagnosis of sarcoidosis was identified by the histopathologic evaluation of the tissue specimes obtained by fiberoptic bronchoscopy in 62%, by cutaneous biopsy in 28%, by ocular biopsy in 12%, by mediastinoscopy in 10%, by lacrimal biopsy in 8% and by various other organ biopsies in 24% of the patients, respectively. Sarcoidosis was diagnosed by the presence of non-caseified granulomas at least in two different organs in a compatible clinical setting. Infectious, inflammatory or auotoimmune diseases that may lead to granulomaous inflammation were excluded in the differential diagnosis of the patients. Minor complications developed in 5.6% of the patients associated with the interventional biopsy procedures. To determine the existence of sarcoidosis ocular involvement, fundoscopic, tonometric and biomicroscopic examinations were performed on all patients. Anterior uveitis was found to be the most common (32%) ocular sarcoidosis finding while posterior uveitis and panuveitis were other frequently observed manifestations. Ocular manifestations were the initial finding in 19 patients (9.7%) while 14 subjects (7.1%) had asymptomatic eye involvement. Red eye appeared as the most common eye symptom that developed in 26.4% of the patients. Biopsy of the conjunctiva and lacrimal gland was performed in 20 (12 cases with visible lesions conjunctival lesions) and in 18 patients, respectively. Non-casefied granulomatous inflammation was detected in all patients with apparent lesions by conjunctivl biopsy while diagnostic yield was 42% in cases without observable lesions. Lacrimal gland involvement was identified in 16 patients. Ocular sarcoidosis disease course and site of eye involvement are depicted in table 2 and 3. Exemplary fundus fluorescein angiography eye sarcoidosis findings are shown in figure 1 and 2.

Ocular sarcoidosis course	# of patients (%)
Asymptomatic at admission	14
Symptomatic at initial admission	18
Ocular sarcoidosis in 12 months	20
Ocular sarcoidosis in 12 - 24 months	14
Ocular sarcoidosis in 24 - 48 months	18
Ocular sarcoidosis after 48 months	16

Table 2: *Course of ocular sarcoidosis.*

Localization of ocular sarcidosis	# of patients (%)
Anterior uveitis	30 (15.3)
Posterior uveitis	22 (11.2)
Panuveitis	18 (9.2)
Lacrimal gland	16 (8.2)
Episcleritis	10 (5.1)
Papillitis	9 (4.6)
Retinal venous engorgement	7 (3.6)
Conjunctival granuloma	6 (3.1)
Optic neuritis	3 (1.5)

Table 3: *Localization of ocular sarcoidosis.*

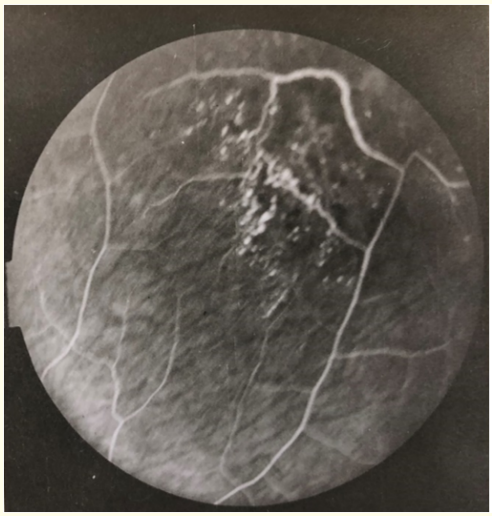

Figure 1: *Periflebilitis, irregular vein walls, dilatation, microaneurysms, and neovascularization (fundus fluorescein angiography) due to sarcoidosis.*

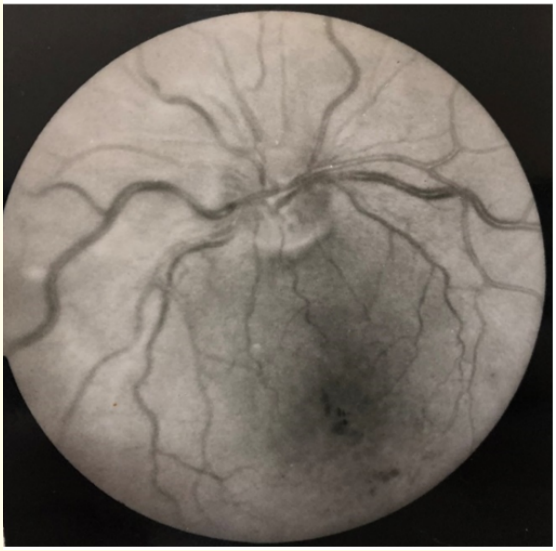

Figure 2: *Edema at the posterior pole, hemorrhagia around macula, venule dilatation, with loss of papillary border (fundus fluorescein angiography) in ocular sarcoidosis.*

Logistic regression with Krukal-Wallis test and Bonferronni corrected two way Mann-Whitney test did not determine any statistical difference in regard to prognosis between the three groups according to age and gender (Table 1). Serum biochemistry values were not distinct (r:0.2, $p < 0.14$) between the three groups. We have not observed any significant difference between the FEV_1, FVC, and TLC percentage values of the three groups (r: 0.3, $p < 0.05$). The lowest DLCO/VA ratios were observed in patients with simultaneous ocular and lacrimal gland involvement. The worst prognosis was observed in patients with simultaneous ocular and lacrimal gland involvement that showed a significantly high correlation (r: 0.86, $p < 0.05$) with the disease outcome. Severe prognosis displayed a moderate correlation (r:64, $p < 0.05$) in patients with ocular involvement without lacrimal sarcoidosis. The best prognosis was observed in the third group of patients without any evidence of ocular disease as the lowest correlation with a severe prognostic outcome (r:0.24, $p < 0.01$) was observed in this group. Disease stage correlated with the simultaneous likelihood of ocular and lacrimal gland involvement existence (r: 0.82, $p < 0.05$) revealing that probability of coexistent ocular and lacrimal gland involvement increased as the sarcoidosis stage progressed.

Discussion and Conclusion

Clinically evident ocular sarcoidosis develops in approximately 20% to 30% of the patients. Uveitis emerges in about one to two thirds and conjunctival nodules are identified in 40% of the sarcoidosis patients. Ocular involvement in sarcoidosis varies from 11.8% to 79% among patients [1-4,6,17,23] and may emerge at any stage of the disease. It may be totally asymptomatic or develops as the initial manifestation of sarcoidosis that may come out at any site of the eye [2-4,19-23]. Data concerning the clinical and prognostic features of ocular and lacrimal gland involvement in sarcoidosis is scarce currently due to the asymptomatic clinical profile along with the absence of a definitive diagnostic criteria. These factors lead to a variable prevalance of ocular sarcoidosis. This conflict consequently leads to insufficient data for the prognostic outcome of sarcoidosis patients with simultaneous ocular and lacrimal gland involvement. Findings of our study indicate that the coexistence ocular and lacrimal gland involvement may be a hallmark marker for defining the prognosis in sarcoidosis.

Identification of simulatenous ocular and lacrimal gland disease appears to be a useful clinical determinant to predict the prognostic consequence or corollary in sarcoidosis patients. As the stage of sarcoidosis progressed the likelihood of coexistent ocular and lacrimal gland involvement increased revealing a significantly high correlation between involvement of these structures and disease stage.

Ocular disease as the initial or subesequent manifestation of sarcoidosis is not rare. This variability depends upon many factors like genetic or racial features of the population, methods and utilities used for diagnostic evaluation [19-23]. It is well-known that ocular involvement is a hallmark of sarcoidosis. Evaluation of prognostic consequences in our study has revealed that simultaneous ocular and lacrimal gland involvement in sarcoidosis appears to be a pivotal precursor for determining the outcome in sarcoidosis patients. Patients with synchronous involvement displayed a significantly worse prognosis compared to patients with ocular disease and to those without any evidence of eye involvement. Our study reveals that identification of ocular sarcoidosis along with lacrimal gland involvement emerges to be an important measure not only as a diagnostic factor for sarcoidosis patients with an indecisive presentation due to single organ involvement but also as a prognostic determinant. Despite the fact that lacrimal gland involvement in sarcoidosis patients appears to be a marker for a benign disease outcome, its association with ocular disease has emerged as a significant indicative factor for chronic and persistent sarcoidosis in our study. Coexistence of such an association appears to be crucial determinant that may alert the clinicians for a chronic prognostic outcome in sarcoidosis patients.

Granuloma formation, evolution, and distribution among pulmonary or extrapulmonary organs determine the prognosis in sarcoidosis patients. Differences of prognosis and organ involvement among individual patients is greatly associated with the inconsistent propensity of granuloma formation and dissemination. The worse prognosis in patients with synchronous ocular and lacrimal gland sarcoidosis is primarily associated with the presence of a higher granuloma burden in this group. As the number of organs involved in sarcoidosis increases, the burden of granulomas will also increase that will adversely effect the prognosis of sarcoidosis. This pathological mechanism may explain the coexistence of ocular and lacrimal gland involvement as a determinant of poor prognosis due to the high granuloma burden. The further excessive granuloma encumbrance is relatively caused by ocular and lacrimal disease in our study is verified by the presence of higher serum ACE levels in these patients. Sarcoidosis treatment targets granuloma supression to preserve organ function and attenuate fibrosis thereby enabling a better prognosis [24-26].

There are some limitations of our study. Small sample size appears as the first limitation. Second, the outcome and prognosis of sarcoidosis patients reveal a significant variation due to the genetic or hereditary factors. Our study group consisted of exclusively Caucasian people while other races may display different outcomes in regard to organ involvement, prognosis and disease course. It is well-known that hereditary and genetic factors in sarcoidosis may cause a great variability for clinical manifestations and prognosis [11,27-29]. It may be considered that the follow-up period of the patients is short but the prognostic risk factors for progressive disease become appearent within the two years of diagnosis while patients with a persistent disease after five years from diagnosis are designated to have a chronic disease [12,30-33]. The mean follow up period was approximately eight years in this study. The distinct prevalance of ocular sarcoidosis is due to patient symptoms, to the extent of ocular disease, and to the criteria used for the diagnosis of ocular sarcoidosis. These factors may have an inverse impact on the results of our study. Further studies with larger sample sizes, different genetic or racial backgrounds, and more heterogenous patient populations are required to determine the precise and accurate effect of coexistent ocular and lacrimal gland involvement on disease prognosis in sarcoidosis.

The results of our study indicate that ocular and lacrimal gland involvement in sarcoidosis is a crucial risk factor for chronic progressive disease. Prevalance of ocular sarcoidosis is highly variable because patients are asymptomatic, different diagnostic criteria are used for identification of ocular sarcoidosis, and in most asymtomatic patients opthalmologic examination is not done. These factors may have adversely effected the prognostic determinant contribution to patient outcome in sarcoidosis. A definitive diagnostic distinction between

chronic persistent sarcoidosis and self-limited disease is very difficult. Although progressive sarcoidosis does not always lead to chronic disease pattern, it is the hallmark or a pivotal step in the treatment of sarcoidosis to determine the factors that predispose to a fibrotic disease beforehand. Diagnosis of ocular sarcoidosis by opthalmologic examination is a beneficial, a simple, and a noninvasive clinical approach both for diagnosis and to predict the probability of a chronic outcome in sarcoidosis. Opthalmologic examination is a practical clinical enterprise for a meticulous follow-up and to determine the treatment options in sarcoidosis patients as a preliminary application that may also be useful for the diagnosis of sarciodosis in equivocal cases but appears to be extremely useful and efficient to predict the prognostic outcome.

Author Contributions

Halil Yanardag prepared the clinical findings of the patients.

Cuneyt Tetikkurt has designed and wrote the manuscript.

Muammer Bilir prepared statistical data analysis of patients.

Halit Pazarlı has laid out the opthalmologic manifestations of the patients.

Emre Yanardag prepared the tables and the references.

Conflicts of Interest

All authors does not have any conflicts of interest to declare associated with this study.

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