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Original Article

A Prospective Review of the Results of Patients Treated and Followed up for a Diagnosis of Sarcoidosis

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Abstract

OBJECTIVES: The present study reports the treatment and follow-up results of patients prospectively diagnosed and treated in a public hospital.

MATERIAL AND METHODS: The present study reports the prospective follow-up data of 21 sarcoidosis cases followed up and treated in the Department of Chest Diseases of Dörtyol State Hospital from January 2010 to December 2014

RESULTS: The 21 cases had a mean age of 44±10 years and a mean follow-up period of 38±13 months. While 10 cases were given steroid treatment, 11 cases were radiologically followed up. Besides pulmonary involvement, skin findings were detected in 7 cases and ophthalmologic findings were detected in 3 cases. In the treatment group, regression was observed in the radiographic findings of 6 cases, while no radiologically significant changes were seen in 4 cases. In the follow-up group, regression was observed in the radiographic findings of 9 cases, while no significant changes were seen in mediastinal LAPs of 2 cases. At the end of the treatment, it was found that 1 case developed steroid-induced myopathy, 1 case developed fungus ball of the sequelae, 1 case had loss of vision secondary to posterior uveitis, and 1 case had a risk of steroid-induced osteoporosis.

CONCLUSION: Choice of treatment procedure based on the stage and clinical results of the patient is still the most effective method in sarcoidosis treatment.

KEYWORDS: Sarcoidosis, treated, diagnosis

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INTRODUCTION

Sarcoidosis is a disease of autoimmune origin with unknown etiology that can affect many organs and systems and is histopathologically accompanied by noncaseating granulomatous inflammation. Sarcoidosis may affect many systems, especially the lungs, skin, eyes, reticuloendothelial system, musculoskeletal system, exocrine glands, and cardiac and nervous systems. Therefore, it requires a multidisciplinary approach in both diagnosis and treatment [1].

The present study reports the treatment and follow-up results of patients prospectively diagnosed and treated in a public hospital.

MATERIAL AND METHODS

The present study reports the prospective follow-up data of 21 sarcoidosis cases followed up and treated in the Department of Chest Diseases of Dörtyol State Hospital, Turkey from January 2010 to December 2014. Demographic features, clinical findings (symptoms, physical examination findings), radiological imaging results (pulmonary radiography, thoracic tomography), laboratory findings (hemogram, glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood calcium, C-reactive protein, sedimentation, skin test results (purified protein derivative (PPD)), interventional diagnostic methods (mediastinoscopy, bronchoscopy, thoracotomy, clinical-radiological), pulmonary function testing (functional vital capacity (FVC), forced expiratory volume (FEV1), and follow-up and treatment results of the patients diagnosed with sarcoidosis were evaluated.

All cases were examined and evaluated by the departments of Ophthalmology, Neurology, and Cardiology for the presence of extrapulmonary involvement.

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Patient Control Protocol

After the diagnosis, the followed up patients visited the clinic for radiological imaging, laboratory testing, pulmonary function testing, cardiac imaging [electrocardiography (ECG)], echocardiography (ECHO), and ophthalmologic consultation every 6 months.

The treated patients visited the clinic at Weeks 1 and 2 and then Months 1 and 12 where consultations were carried out for radiological imaging (Months 1, 3, 6, 9, and 12), laboratory testing (Months 1, 3, 6, 9, and 12), pulmonary function testing (every 3 months), cardiac imaging (ECG and ECHO every 6 months), ophthalmic examination (every 6 months), and physiotherapeutic measurement (bone density measurements in the beginning and at the end of the study period).

Patient Treatment Protocol

Bronchodilator Therapy

Formeterol/Budesonid 12/400 µg was administered to the symptomatic cases (cough, wheezing, shortness of breath) and/or to the cases with a positive reversibility (a 12% or 200 (mlt) increase in FEV1) in pulmonary function testing.

Corticosteroid Therapy

Of the patients with pulmonary involvement, corticosteroid (CS) therapy was given to the ones with symptomatic progressive pulmonary function loss, asymptomatic progressive function loss, or permanent infiltrations. Of the cases with extrapulmonary involvement, it was given to the ones with lupus pernio, neurosarcoidosis (except for isolated cranial nerve palsy), eye involvement refractory to local treatment, cardiac involvement (cardiomyopathy, arrhythmia, AV block), and symptomatic hypercalcemia. Of the followed up patients, it was given to the ones who had not spontaneously recovered within 6 months and who had symptoms (uncontrollable with inhalers, CSs, or bronchodilators) and low pulmonary function test results.

The cases other than these were followed up.

The initial dosage of methyl prednisolone was 32-48 mg/day. At the end of Month 2, it was reduced to 16 mg/day, which was then adjusted to be 8 mg/day as the maintenance dose for the rest of the year. In the CS therapy group, the ones with positive PPD (>15 mm) were given isoniazid prophylactic therapy for 6 months.

The study was planned according to the World Medical Association Declaration of Helsinki (2013). Written informed consent was obtained from patients who participated in this study.

The IBM Statistical Package for Social Sciences version 23 software (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Descriptive statistics for continuous variables are presented as digital and for categorical variable are presented as percentages.

RESULTS

The mean age of the 21 cases (female/male: 16/5) was 44±10 years (min: 27, max: 68), and the mean follow-up period was 38±13 months (min: 10, max: 62). Radiologically, findings of 12 cases were consistent with Stage 1 (Figure 1a-c), findings of 5 cases were Stage 2 (Figure 2a-b), and findings

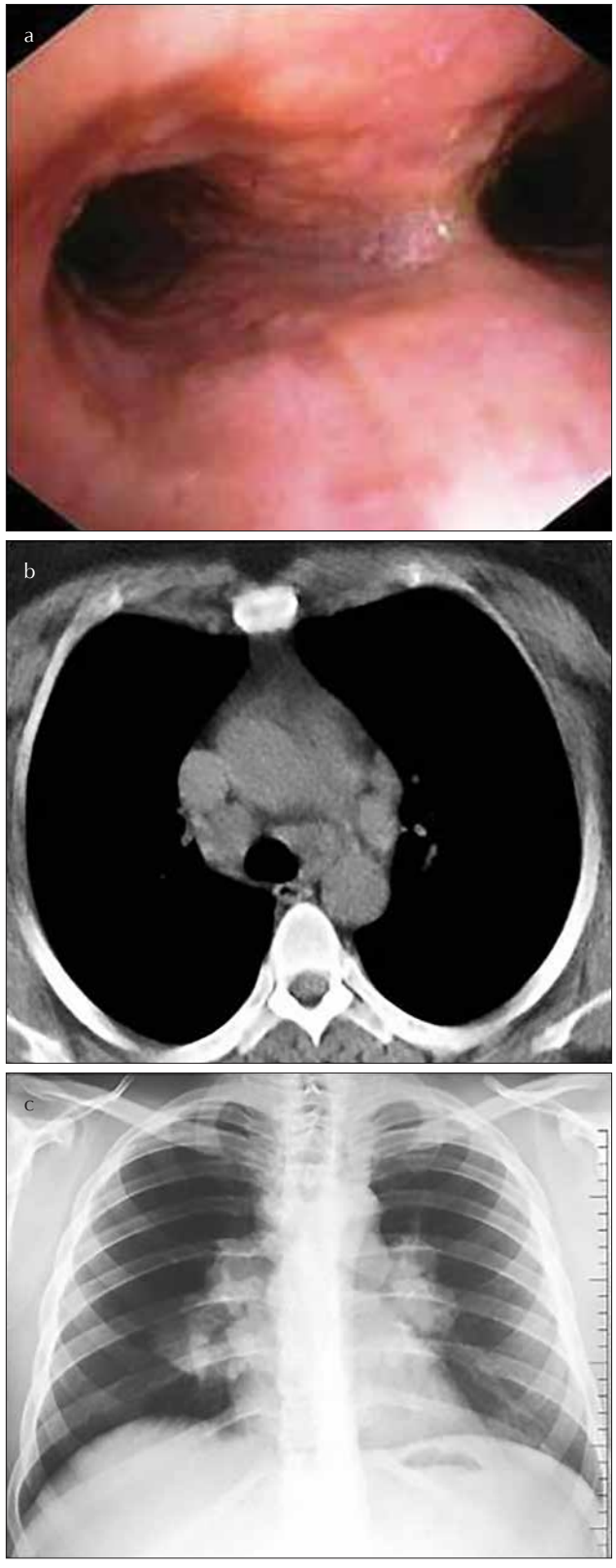

Figure 1. a-c. Stage 1 sarcoidosis

of 4 cases were Stage 3 (Figure 3). Of the cases, 10 were diagnosed using mediastinoscopy, 5 with bronchoscopy, 3 with thoracotomy, and 3 with clinical radiology (Table 1). The most common symptoms were cough (n=18), wheezing (n=15), and shortness of breath (n=12). In the follow-up group, wheezing/rhonchus was detected in 5 cases, while no auscultation findings were detected in 6 cases. In the treatment group, inspiratory rales were detected in 6 cases, while wheezing/rhonchus was detected in 8 cases (Table 2). While 10 cases were given steroid treatment, 11 cases were radiologically followed up. In the treatment group, 2 cases were

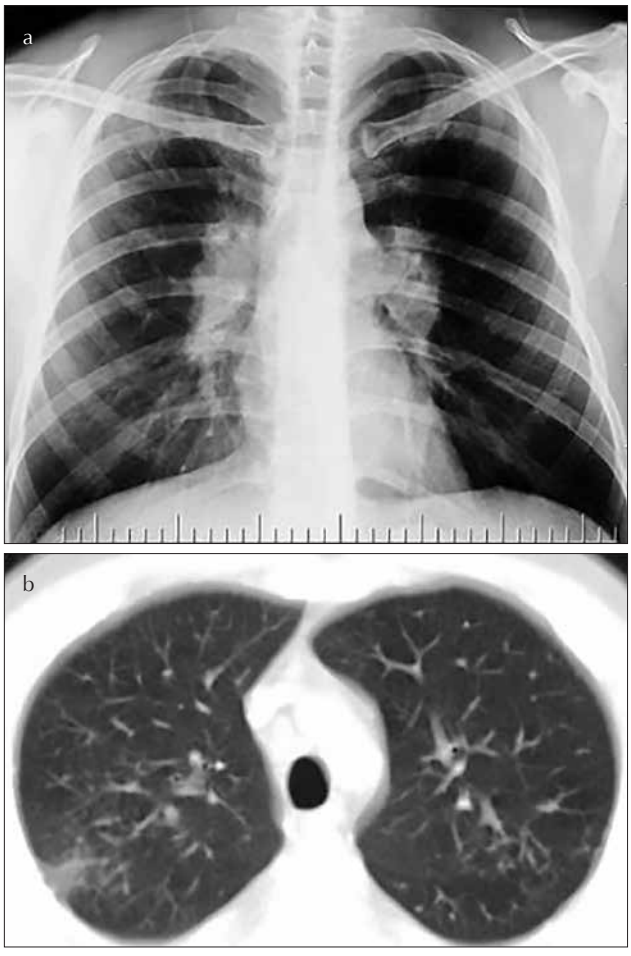

Figure 2. a,b. Stage 2 sarcoidosis

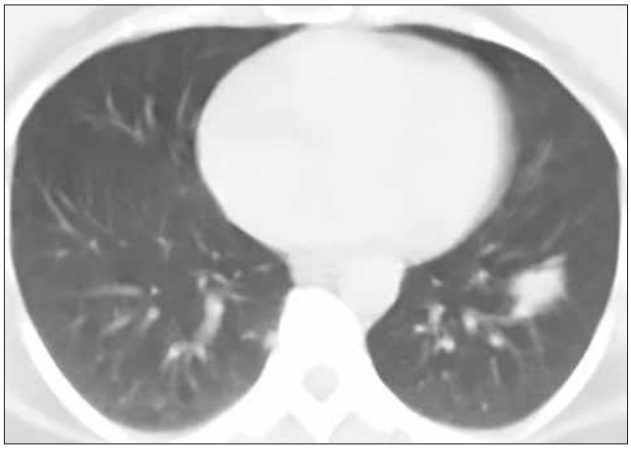

Figure 3. Stage 3 sarcoidosis

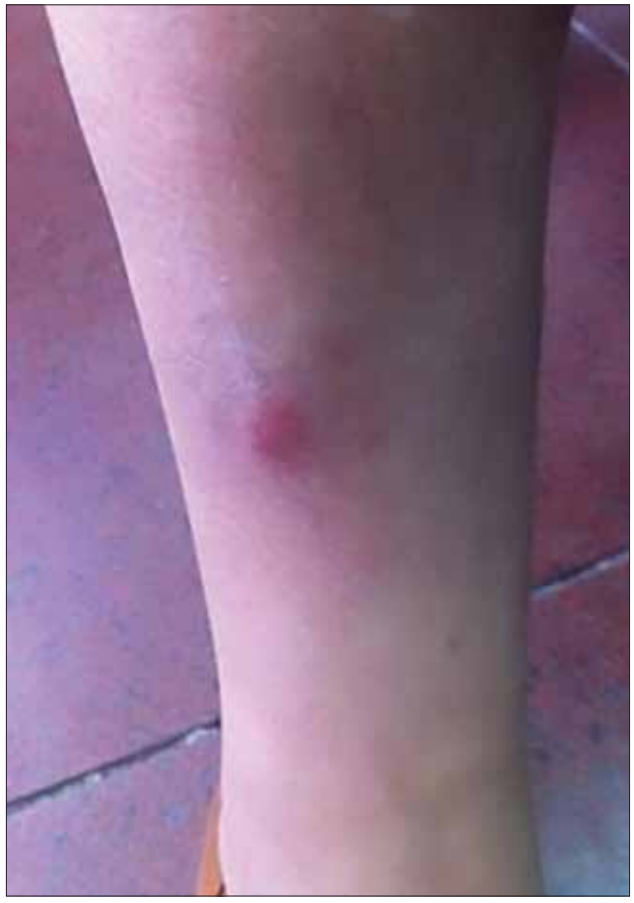

Figure 4. Erythema nodosum

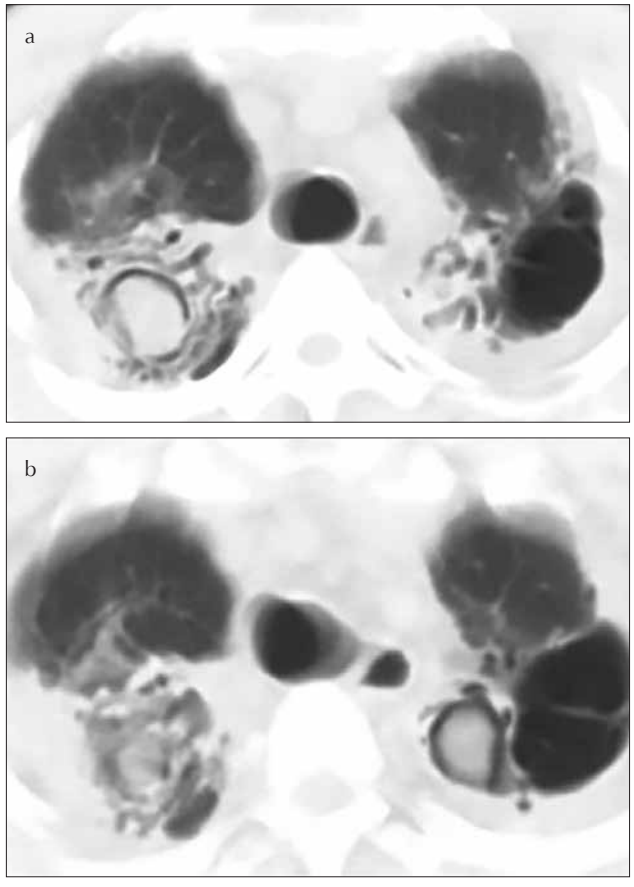

Figure 5. a,b. Fungus ball

Table 1. Diagnostic methods and stages of the sarcoidosis cases

Diagnostic Method	Number (n)	Ratio (%)
Mediastinoscopy	10	48
Bronchoscopy	5	24
Thoracotomy	3	14
Clinical-Radiological	3	14
Stage		
Stage 1	12	58
Stage 2	5	23
Stage 3	4	19

Table 2. Symptoms and auscultation findings of the sarcoidosis cases

Symptoms	Number of Treated Cases (n)	Number of Followed Up Cases (n)
Cough	10	8
Wheezing	10	5
Shortness of breath	9	3
Weakness	3	2
Phlegm	2	1
Chest pain	0	2
Hemoptysis	1	1
Muscle pain	1	1
Back pain	1	1
Difficulty swallowing	0	1
Joint pain	0	1
Fever	1	0
Auscultation Finding		
Wheezing/rhonchus	8	6
Rale	6	0
Normal	0	5

Table 3. Pulmonary function testing results of the treated patients before follow-up and after the last control visit

	Before follow-up FVC/%	Before follow-up FEV1/%	After follow-up FVC/%	After follow-up FEV1/%
Case 1	1.69/65	1.50/68	2.50/116	2.02/112
Case 2	5.61/111	5.56/115	5.15/111	4.19/106
Case 3	2.19/84	1.62/74	2.33/108	1.88/108
Case 4	4.43/132	4.02/137	3.96/110	3.33/107
Case 5	2.45/99	1.92/92	2.61/109	2.60/110
Case 6	2.04/85	2.00/84	2.77/104	2.22/98
Case 7	2.56/102	2.00/100	3.64/115	2.92/107
Case 8	2.06/89	2.00/98	2.20/111	1.88/108
Case 9	2.85/96	2.54/100	3.45/122	3.02/125
Case 10	2.96/80	2.32/72	3.01/87	2.62/98
Case 11	2.78/92	2.58/104	2.88/101	2.37/97

FVC: functional vital capacity; FEV1: forced expiratory volume 1

Table 4. Pulmonary function testing results of the treated patients before treatment and after the last control visit

	Pre-treatment FVC / %	Pre-treatment FEV1 / %	Post-treatment FVC / %	Post-treatment FEV1 / %
Case 1	4.32/79	2.90/66	5.49/99	4.96/105
Case 2	2.63/83	2.02/73	3.28/111	2.89/114
Case 3	2.62/92	1.74/72	3.58/128	2.00/103
Case 4*	2.55/72	2.14/70	3.98/112	3.69/120
Case 5	2.49/70	1.76/60	3.61/121	2.56/102
Case 6**	3.55/81	3.40/93	5.30/123	4.32/123
Case 7	2.00/78	1.98/68	2.59/92	2.03/85
Case 8	3.53/89	2.80/68	3.98/102	3.50/98
Case 9	2.97/63	2.53/65	4.59/101	3.23/86
Case 10	2.92/91	2.13/77	4.04/134	2.75/110

FVC: functional vital capacity; FEV1: forced expiratory volume 1
*Case treated for endobronchial sarcoidosis
**Case treated for posterior uveitis

Stage 1, 5 cases were Stage 2, and 3 cases were Stage 3, while 10 cases were Stage 1 and 1 case was Stage 3 in the follow-up group. In the treatment group, the initial mean FVC was 2.95±0.6 mlt (79.8%±9.5%) and FEV1 was 2.34±0.5 mlt (71.2%±8.9%) (Table 3). In the follow-up group, the initial mean FVC was 2.86±1.2 (95.4%±17.7%) and FEV1 was 2.61±1.2 (97.4%±19.9%) (Table 4). Besides pulmonary involvement, skin findings (erythema nodosum) (Figure 4) were detected in 7 cases and ophthalmologic findings were detected in 3 cases (previous anterior uveitis in 2 cases and posterior uveitis in 1 case). In the treatment group, regression was observed in the radiographic findings of 6 cases, while no radiologically significant changes were seen in 4 cases. In the follow-up group, regression was observed in the radiographic findings of 9 cases, while no significant changes were seen in mediastinal LAPs of 2 cases. At the end of the treatment, it was found that 1 case developed steroid-induced myopathy, 1 case developed fungus ball of the sequelae (Figure 5a-b), 1 case had loss of vision secondary to posterior uveitis, and 1 case had risk of steroid-induced osteoporosis.

DISCUSSION

In an epidemiologic study carried out in Turkey, the annual incidence of sarcoidosis was found to be 4 in 100,000 [2]. Studies on sarcoidosis were retrospectively evaluated while the cases were monitored and followed up prospectively from diagnosis to the end of the treatment and follow-up period in our study. This paper discusses the follow-up and treatment features of the treated and followed up patients rather than the clinical, laboratory, and radiological findings of sarcoidosis patients.

Sarcoidosis treatment seeks to answer the questions of when and why. It is hard to determine when to initiate the treatment because the natural course of sarcoidosis is highly variable and the benefits of early treatment are yet to be accepted. Today, CSs are the first drugs to be preferred in the first-step treatment of sarcoidosis. Real indications, doses, and treatment periods of CSs and their effects on the natural course of

disease are yet to be clarified. The recent increase in steroid-reducing medicines has led to an increase in treatment options. While there is contradictory information about inhaled CSs (ICSs), these usually have a limited role in the control of symptomatic pulmonary sarcoidosis. Budesonide is the most studied steroid [3,4]. A randomized, double-blinded, and placebo-controlled study including 189 newly diagnosed Finnish patients found that the actively treated patients showed a medium pulmonary function recovery and had fewer relapses after 5 years [5]. Our current knowledge about ICSs shows that their main role is the treatment of cough or bronchospasm [3]. In our study, 5 patients in the follow-up group who were symptomatic (cough, wheezing, shortness of breath, etc.) and/or showed reversibility in pulmonary function testing after diagnosis were given bronchodilator (formoterol/budesonide 12/400 µg) therapy. Full symptom control was achieved at the end of Month 8 after bronchodilator therapy was initiated. Bronchodilator therapies of the patients in the follow-up group were withdrawn as the stepwise treatment of asthma. In the follow-up group, regression was observed in the radiographic findings of 9 cases (within Months 6-9 of follow-up), while no significant changes were seen in mediastinal LAPs of 2 cases. In the treatment group, 8 cases were given bronchodilator therapy (formoterol/budesonide 12/400 µg) before CS therapy.

Corticosteroid therapy is recommended for patients who have progressive pulmonary involvement, asymptomatic progressive pulmonary function loss or permanent infiltrations, lupus pernio, neurosarcoidosis (except for isolated cranial nerve palsy), eye involvement refractory to local treatment, cardiac involvement (cardiomyopathy, arrhythmia, AV block), and symptomatic hypercalcemia and for the ones who do not spontaneously recover within 6 months of follow-up and who have symptoms (uncontrollable with inhalers, CSs, and bronchodilators) and low pulmonary function testing results. There is no clear consensus on optimal dose. However, most specialists initiate the treatment with a dosage of 20–40 mg/day, which is maintained for 1-3 months. It is important that steroid dose is reduced to the minimum dose sufficient to control the symptoms. Although some researchers state that a prednisone dose of ≤10 mg a day is the sufficient (target) dose for maintenance, the maintenance dose should be determined for each patient individually [6]. Maximum recovery occurs within 3-4 weeks in pulmonary sarcoidosis, and the daily dose can be reduced to the maintenance dose within 1-3 months [7,8].

We administered CS therapy to 10 of our cases. We directly initiated CS therapy for 2 cases in the treatment group (because one of the cases had posterior uveitis while the other had endobronchial lesions and severe symptoms). The remaining 8 cases were initially given bronchodilator therapy (formoterol/budesonide 12/400 µg). Treatment was administered to 1 patient for becoming symptomatic (within Month 9 of follow-up) with symptoms uncontrollable with bronchodilator therapy by transitioning from Stage 1 to Stage 2 in the clinical, radiological, and SFT follow-up results, while 7 cases were treated for having low pulmonary function test results during follow-up and a high frequency of presenting to the emergency department or outpatient clinics due to increased symptoms despite bronchodilator therapy (within Months 5-8 of follow-up). The initial prednisolone dose was 48 mg/day for 2 cases, while it was 32 mg/day for 8 cases, all of which were reduced to 16 mg/day at the end of Month 2 and to 8 mg/day at the end of Month 3, which was maintained for the rest of the year. At the end of the treatment period, regression was observed in the radiographic findings of 6 cases (full regression in 5 cases and partial regression in 1 case), while no radiologically significant change was seen in 4 cases. A remarkable improvement was detected in clinical and pulmonary function testing of all cases. At the end of the treatment period, 1 case developed fungus ball of sequelae, 1 case developed steroid-induced myopathy, and 1 case developed risk of steroid-induced osteoporosis.

Steroid-reducing immunoregulatory drugs are contraindicated for patients with CS intolerance, disease progression despite sufficient steroid therapy (15 mg/day prednisone therapy for a minimum of 3 months), and continued disease despite long-term and high-dose CS therapy (prednisone ≥15 mg/day) [9]. None of the treated patients needed steroid-reducing immunoregulatory drugs.

Another important issue is the bone health of the patients taking CS therapy. Even low doses such as 5 mg/day may cause remarkable bone loss, and the severity of bone loss is correlated with the overall cumulative dose. Guidelines for preventing and treating glucocorticoid-induced osteoporosis advise that bone density measurements be taken of patients under CS treatment and bisphosphonate therapy in the first-step treatment and as part of primary care for high-risk groups (e.g., patients over 65 or with a history of bone fracture) [10,11]. Bone density measurements were performed in 10 cases given CS therapy both at the beginning and end of the treatment period. One case was given risedronate sodium therapy due to the indication of osteoporosis risk in the bone density measurement at the end of the treatment.

It is recommended that a skin test (PPD) be performed for latent tuberculosis in the patients before initiating CS therapy [3]. We performed the PPD test for latent tuberculosis in all of our cases. In the CS therapy group, 8 cases were given a 6-month isoniazid prophylaxis due to a PPD>15 mm.

In conclusion, choice of treatment procedure based on the stage and clinical results of the patient is still the most effective method in sarcoidosis treatment. The followed up symptomatic patients should certainly be given bronchodilator therapy. Furthermore, it was shown that treatment success can be increased by individualization and close follow-up of the standard treatment procedure. Patient-specific treatment services and follow-up approaches should be increased, especially for idiopathic chronic diseases having alternate drug treatments.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - L.Ö., B.Ö.; Design - L.Ö., B.Ö.; Supervision - L.Ö., B.Ö.; Resource - L.Ö., B.Ö.; Materials - L.Ö., B.Ö.; Data Collection and/or Processing - L.Ö.; Analysis and/or Interpretation - L.Ö.; Literature Search - L.Ö.; Writing - L.Ö.; Critical Reviews - L.Ö.

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Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Akabay Ö. Current Approach to the Diagnosis and Treatment of Sarcoidosis. Güncel Göğüs Hastalıkları Serisi 2014;2:379-86. [CrossRef]
2. Musellim B, Kumbasar OO, Ongen G, et al. Epidemiological features of Turkish patients with sarcoidosis. Respir Med 2009;103:907-12. [CrossRef]
3. Şimşek A, Ofluoğlu R, Hoca NT. Treatment of Sarcoidosis. Solunum Hastalıkları 2010;21:104-13.
4. Lazar CA, Culver DA. Treatment of Sarcoidosis. Semin Respir Crit Care Med 2010;31:501-18. [CrossRef]
5. Pietinalho A, Tukiainen P, Haahtela T, et al. Oral prednisolone followed by inhaled budesonide in newly diagnosed pulmonary sarcoidosis: a double-blind, placebocontrolled multicenter study. Chest 1999;116:424-31. [CrossRef]
6. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: a delphi consensus study. Respir Med 2010;104:713-23. [CrossRef]
7. Judson MA. An approach to the treatment of pulmonary sarcoidosis with corticosteroids: the six phases of treatment. Chest 1999;115:1158-65. [CrossRef]
8. Goldstein DS, Williams MH. Rate of improvement of pulmonary function in sarcoidosis during treatment with corticosteroids. Thorax 1986;41:473-4. [CrossRef]
9. King CS, Kelly W. Treatment of sarcoidosis. Dis Mon 2009;55:704-18. [CrossRef]
10. Schutt AC, Bullington WM, Judson MA. Pharmacotherapy for pulmonary sarcoidosis: a delphi consensus study. Respir Med 2010;104:713-23. [CrossRef]
11. Van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-inducedosteoporosis: a meta-analysis. Osteoporos Int 2002;13:777-87.[CrossRef]