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# Perspective of sarcoidosis in terms of rheumatology: a single-center rheumatology clinic experience

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## Abstract

Sarcoidosis may present with many rheumatological symptoms as well as mimic and/or may occur concomitantly with many other rheumatic diseases. We examined the demographic, clinical and laboratory characteristics of patients diagnosed with sarcoidosis in the rheumatology department. This study planned as retrospective cross-sectional study. Medical records of patients who applied to our rheumatology outpatient clinic due to complain of musculoskeletal problems and then diagnosed sarcoidosis were retrospectively investigated. Joint findings, extrapulmonary involvements, and coexisting rheumatic disease were evaluated. Fifty-six patients (41.21 ± 7.83 years, 75% female) were included. The duration of the disease was 49.61 ± 29.11 months, and the follow-up period was 26.66 ± 13.26 months. All patients had pulmonary system involvement. Arthralgia was present in 91.10% of 56 patients and arthritis in 89.29% of patients. Examining the subtypes of the arthritis findings, mono-arthritis was found in 31/50 (62%) patients, oligo-arthritis in 15/50 (30%) patients, and polyarthritis in 4/50 (8%) patients. A total of 11 (19.60%) patients were diagnosed with uveitis. Excision of the mediastinal LAP was performed in a total of 37 patients (66.1%) and became the most commonly employed method. Considering the treatment distribution of the patients under followed-up, it is seen that non-steroidal anti-inflammatory treatments were used in 15 (26.8%) patients, corticosteroids in a total of 40 (71.4%) patients, methotrexate in a total of 15 patients (26.8%), azathioprine in six (10.7%) patients, hydroxychloroquine in 14 (25%) patients, and infliximab in one (1.8%) patient. As sarcoidosis is a mimicking disease, a good differential diagnosis should be made to avoid misdiagnosis and in order not to be late in diagnosis and treatment. Physicians, especially rheumatologists, should remember sarcoidosis more frequently as the disease may overlap with other rheumatological diseases and may occur with many rheumatological manifestations.

**Keywords** Sarcoidosis · Organ ınvolvement · Arthritis · Uveitis

## Introduction

Sarcoidosis is a rare, multisystemic chronic disease of unknown cause, characterized by the formation of non-caseating granulomas, and is often characterized by bilateral hilar lymphadenopathy, pulmonary infiltration, cardiac involvement, eye and skin lesions [1, 2]. Sarcoidosis has been reported more frequently in female patients and mainly affects the ages of 20–40. Its incidence in Turkey has been reported as 4/100000 [3, 4]. Depending on the genetic background, the systems primarily affected may differ. In addition to lung involvement, especially erythema nodosum and joint involvement were observed in studies conducted in Turkey, and other organ involvements are very rare [3, 4]. Pulmonary involvement, the most critical finding of the disease, may be silent or present with respiratory distress or cough. In the presence of clinical and laboratory conditions consistent with radiological hilar or interstitial involvement, sarcoidosis should be considered [1, 5–7]. Since it is multisystemic, it often has clinical and laboratory features similar to many infectious, malignant and rheumatic diseases, and may cause differential diagnosis [8, 9]. The prognosis of the disease

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depends on its onset and degree [1, 2, 10]. Although deaths related to sarcoidosis differ between countries, the mortality rate in patients with untreated sarcoidosis has been reported to be 5% [10–12]. Although there are no universal criteria for the diagnosis of the disease, the diagnosis is made based on clinical findings, radiological findings, histopathological demonstration of non-caseating epithelioid granulomas in the tissue, and rule out conditions of granulomatous character with similar characteristics [13–15]. Despite not being specific, serum ACE, serum calcium levels, and if possible, an increase in CD4/CD8 ratio obtained in bronchoalveolar lavage may assist the diagnosis [16–18]. As sarcoidosis is mostly a rule-out diagnosis, a strong differential diagnosis must be made [8].

Sarcoidosis may present with many rheumatological symptoms as well as mimic and/or may occur concomitantly with many other rheumatic diseases including ankylosing spondylitis (AS), rheumatoid arthritis, and Sjögren's syndrome [8]. It should be kept in mind as a differential diagnosis in patients applying to the rheumatology outpatient clinic, and patients diagnosed with sarcoidosis should be evaluated in detail in terms of systemic involvement. The aim of this study was to document the demographic, clinical and laboratory characteristics of patients diagnosed with sarcoidosis in our clinic between 2014 and 2021, investigate the distribution frequency of rheumatological findings, and identify other accompanying rheumatological diseases if any.

## Methods

This study was planned as the retrospective and cross-sectional study. Approval for the study was obtained from the Committee on Human Research Ethics of Ankara State Hospital (dated: 31 March 2020, decision number: E1-21–1662). In our rheumatology department, detailed anamnesis is taken from each patient and standard systemic and rheumatological examinations are performed. Joint involvement is assessed by the presence of soft tissue swelling and effusion (number of swollen joints) and tenderness with movement or touch (number of tender joints). Ultrasonography is used in patients with suspected arthritis but whose diagnosis cannot be confirmed by physical examination. All patients with suspected sarcoidosis undergo chest radiograph and, if necessary, high-resolution computed tomography to evaluate lung involvement. A detailed neurological examination is performed in terms of neurological involvement and an ophthalmologist is consulted for a detailed eye examination. After the diagnosis of sarcoidosis is confirmed, the treatment of the patients is planned according to the organ involvement.

Medical records of patients who applied to our rheumatology outpatient clinic between 2014 and 2021 due to complain of musculoskeletal problems and then diagnosed sarcoidosis were retrospectively investigated. Patients diagnosed with sarcoidosis by the same rheumatologist based on compatible clinical-radiological data and histological evidence of non-caseating granulomas were included. Patients with conditions that may cause granulomatous disease (such as bacterial, fungal, parasitic and fungal infections, foreign body reaction, silicosis, granulomatous polyangiitis, and polyarteritis nodosa) were excluded. A total of 56 sarcoidosis patients were included. Anamnesis, rheumatological inquiries, systemic and locomotor system examination findings, demographic, clinical, radiological, serological, laboratory and histopathological findings were extracted from medical record. Single joint involvement was defined as monoarthritis, 2–3 as oligoarthritis, and five or more joint involvement as polyarthritis. Presence or history of active erythema nodosum and also presence of sequelae, eye and neurological involvement were noted. Diagnosis of concomitant rheumatic disease was determined according to the diagnostic criteria of the involved diseases. Radiographic staging of sarcoidosis is based on the presence of hilar/mediastinal lymphadenopathies and/or lung infiltration without or with fibrosis. Chest radiographs were classified using the modified Scadding staging system. The first preferred medical treatments after the diagnosis were also recorded.

## Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) program version 11.0 for Windows (SPSS Inc., Chicago, IL). Visual and analytical methods were used to determine whether the variables were normally distributed. Normally distributed continuous variables are expressed as mean ± SD, non-normally distributed parameters as median values with inter-quantile range (IQR) (25th and 75th percentiles) values and categorical variables as numbers and percentages.

## Results

When the 56 cases included in the study were evaluated, it was found that the mean age of the patients was 41.21 ± 7.83 years (range: 24–56 years), that the duration of the disease was 49.61 ± 29.11 months (range: 9–110 months), and the follow-up period was 26.66 ± 13.26 months. When evaluated in terms of sex, the female/male distribution was 42 (75%) and 14 (25%), respectively.

When we evaluated the patients in terms of laboratory parameters, the C-reactive protein (CRP) levels of the patients were found to be 15.11 ± 14.75 (median: 9.8, IQR: 17.03), and the mean erythrocyte sedimentation rate (ESR) levels were found to be 42.88 ± 21.89 (median: 41, IQR: 39.75). On the other hand, seven (12.5%) patients were RF positive, seven (12.5%) patients had anti-CCP positive, five (8.9%) patients were ANA positive, and they had elevated anti-SSA. Demographic characteristics and laboratory data of the patients are shown in detail in Table 1.

The acute form of the disease, known as Löfgren syndrome, constitutes 12.5% of our patients.

The self-limiting nature of the disease was also observed in our patients, and the disease regressed in four patients within 6 months. NSAIDs were used for acute sarcoidosis observed in our patients, and no recurrence was observed in any of them. Serum ACE levels were found to be high in 39.2% of our patients with acute sarcoidosis while they were normal in other patients.

## Joint findings

There were arthralgia complaints in 51 (91.10%) of 56 patients whose sarcoidosis diagnosis was validated. In addition, arthritis were detected in 50 (89.29%) patients. Examining the subtypes of the arthritis findings, mono-arthritis was found in 31/50 (62%) patients, oligo-arthritis in 15/50 (30%) patients, and polyarthritis in 4/50 (8%) patients.

**Table 1** Demographic and laboratory characteristics

| Characteristics | |
|---|---|
| Age, average (year) | 41.21 ± 7.83 |
| Sex (female/male) | 42 (75%)/14 (25%) |
| Disease duration, mean (months) | 49.61 ± 29.11 |
| Follow-up duration, mean (months) | 26.66 ± 13.26 |
| RF positivity, *n* (%) | 7 (12.5%) |
| Anti-CCP positivity, *n* (%) | 7 (12.5%) |
| ANA positivity, *n* (%) | 5 (8.9%) |
| Anti-SSA positivity, *n* (%) | 5 (8.9%) |
| CRP, mean ± SD (mg/dL) | 15.11 ± 14.75 |
| Sedimentation, mean ± SD | 42.88 ± 21.89 |
| Elevated vitamin D, *n* (%) | 5 (8.9%) |
| Hypercalcemia, hypercalciuria n (%) | 1 (1.8%) |
| Serum ACE | Normal: 34 (60.7%); high: 22 (39.3%) |
| Classification by thoracic CT involvement, *n* (%) | |
| *Stage 1* | 14 (25) |
| *Stage 2* | 31 (55.4) |
| *Stage 3* | 9 (16.1) |
| *Stage 4* | 2 (3.6) |

Examining the affected joints of 50 patients who developed arthritis, involvement of the small joint of the foot was observed in five patients (10%), the ankle in 35 patients (70%), the knee joint in 14 patients (28%), the wrist in seven patients (14%), and the small joints of the hand in two patients (4%).

## Concomitant rheumatologic disease

Although sarcoidosis is an exclusion criterion, two patients fulfilled the 2016 the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification criteria for primary Sjögren's syndrome [19]. In addition, one patient was classified as ankylosing spondylitis according to the modified New York classification criteria [20].

## Pulmonary involvements

All patients had pulmonary system involvement. When the distribution was examined, it was determined that 14 (25%) patients had Stage I, 31 (55.4%) patients had Stage II, nine (16.1%) patients had Stage III, and two (3.6%) had Stage IV involvement.

## Other extrapulmonary involvements

As our series included sarcoidosis patients diagnosed after admission to the rheumatology outpatient clinic, almost all patients had joint or skin findings. Tenosynovitis was seen in seven (12.50%) patients, while erythema nodosum was one of the most common involvements ($n = 22$, 39.30%). Eye involvement was also prominent as quite a common complaint. A total of 11 (19.60%) patients were diagnosed with uveitis. Although small in number, neurological involvement was observed in two (3.6%) patients and myositis in one (1.8%) patient. Details of the joint and other involvements of the patients are provided in Table 2.

## Lymphadenopathy excision sites and diagnostic methods applied

Fifty-two patients were diagnosed with biopsy from lymph node biopsy, lung or skin. In four patients, sarcoidosis was diagnosed clinically based on typical findings of locomotor involvement and increased serum level of angiotensin-converting enzyme. Excision of the mediastinal lymphadenopathy was performed in 37 patients (66.1%) and became the most commonly employed method. On the other hand, excision of the axillary LAP was performed in eight (14.3%) patients, skin biopsy was performed in three patients (5.4%), excision of the cervical LAP was performed in two patients (3.6%), and excision of the mediastinal LAP and lung

**Table 2** Extrapulmonary involvement areas in sarcoidosis patients

| Extrapulmonary ınvolvement areas | Patients *n* (%) |
|---|---|
| Arthralgia | 51 (91.10) |
| Arthritis | 50 (89.29) |
| *Mono-arthritis* | 31/50 (62) |
| *Oligo-arthritis* | 15/50 (30) |
| *Poli-arthritis* | 4/50 (8) |
| Tenosynovitis | 7 (12.50) |
| Erythema nodosum | 22 (39.30) |
| Uveitis | 11 (19.60) |
| Neurological ınvolvement | 2 (3.6) |
| Myositis | 1 (1.8) |

parenchyma was performed in two patients (3.6%). A total of four (7.1%) patients were not subjected to a procedure. Lymphadenopathy excision sites and diagnostic methods are shown in Table 3.

### First-line preferred treatments after diagnosis

Considering the treatment distribution of the patients after diagnosis, it is seen that non-steroidal anti-inflammatory treatments were used in 15 (26.8%) patients, corticosteroids in a total of 40 (71.4%) patients, methotrexate in a total of 15 patients (26.8%), azathioprine in six (10.7%) patients, hydroxychloroquine in 14 (25%) patients, and infliximab in one (1.8%) patient. The treatment details of the patients are shown in Table 4.

## Discussion

Sarcoidosis, a systemic disease, can be observed in a wide range from an abnormal appearance on chest X-ray detected incidentally in asymptomatic patients to severe organ involvement findings. In addition, it is known that sarcoidosis is diagnosed when they apply to the rheumatology outpatient clinic with extrapulmonary rheumatological complaints [21–24]. Locomotor involvement is seen in 15–25% of patients with sarcoidosis [8, 24, 25]. Rheumatological involvement of sarcoidosis may be accompanied by general constitutional symptoms, sicca complex findings, fibromyalgia or chronic fatigue findings, or it may present with arthropathy or myopathy findings directly involving the joints or causing direct changes in the bone [24–26]. In our study, 51 (91.10%) of 56 sarcoidosis patients had arthralgia, and 50 (89.29%) had arthritis. When the literature is examined, it is reported that arthralgia is the most common complaint with 70%, and the incidence of arthritis is 25% [8, 23, 27]. The patients in our study who applied to the rheumatology outpatient clinic with musculoskeletal complaints reflect the disease spectrum in which rheumatological complaints are common. In our study, it is thought that the increased rates of arthritis are associated with the use of musculoskeletal ultrasonography in addition to physical examination.

When we looked at the joint distribution of our patients with acute sarcoidosis and joint involvement, we observed that most cases had extensive joint involvement. Analyzing the subtypes of arthritis findings, 26% of patients had mono-arthritis, 56% had oligo-arthritis, and 18% had polyarthritis. It is essential to suspect sarcoidosis in patients with extensive joint involvement and oligo-arthritis.

Historically, sarcoidosis was initially thought to be a skin disease; then it was understood to be a systemic disease [28–30]. Specific and non-specific skin lesions may occur at the onset or during sarcoidosis [30–33]. Lupus pernio, a specific disease finding, was not observed in the patients in our study group. In our study, erythema nodosum was one of the most common involvements (39.30%). It draws attention as one of the findings that occur at the admission or during the disease of patients with sarcoidosis. In a study conducted in Turkey, the frequency of skin involvement in sarcoidosis was stated as 33%. The same study reported that it constituted 20% of the patients with erythema nodosum skin involvement [3, 8, 31]. In our series, three patients were diagnosed with sarcoidosis after a skin biopsy of the erythema nodosum. No bone involvement, the frequency of which is 1–15% in the literature [24–26] was observed in our series.

In the literature, asymptomatic muscle involvement due to sarcoidosis has been reported in the range of 20%-80%,

**Table 3** Lymphadenopathy excision sites and diagnostic methods applied

| | Patients, *n* (%) |
|---|---|
| Mediastinal LAP | 37 (66.1) |
| Axillary LAP | 8 (14.3) |
| Skin biopsy | 3 (5.4) |
| Cervical LAP | 2 (3.6) |
| Mediastinal LAP and lung parenchyma | 2 (3.6) |
| Not performed | 4 (7.1) |

**Table 4** Distribution of drugs used in treatment

| Drug name | Patients *n* (%) |
|---|---|
| Non-steroidal anti-inflammatory | 15 (26.8) |
| Corticosteroids | 40 (71.4) |
| Methotrexate | 15 (26.8) |
| Azathioprine | 6 (10.7) |
| Hydroxychloroquine | 14 (25) |
| Infliximab | 1 (1.8) |

while symptomatic involvement has been reported to be approximately 0.5–5% [24, 25, 34, 35]. Although muscle biopsy was not performed in our patient who was diagnosed with sarcoidosis, myopathic involvement was observed in a patient with increased muscle enzymes and confirmed EMG findings. He responded well to the systemic steroid and methotrexate combination treatment, and it was observed that the involvement regressed in line with the course of the disease.

Neurological involvement can be found at a rate of 5–20% as a sign of extrapulmonary involvement without systemic and pulmonary involvement. Neurosarcoidosis can be asymptomatic or present with severe neurological symptoms. Headache is the most common symptom of the disease. Neurosarcoidosis may present with peripheral and central system involvements or occupational lesions of the intracranial cavity, as presented in the literature [36–38]. In this study, two patients were diagnosed with neuro-sarcoidosis because they had histopathological sarcoidosis. Neurosarcoidosis was considered because the first patient had bilateral facial nerve palsy and the second patient had optic nerve involvement. The diagnosis was confirmed after cranial MRI and ophthalmologic and neurological consultations. The most common cranial neuropathy of neuro-sarcoidosis is bilateral facial nerve involvement [36–38]. Additionally, in the literature, it is acknowledged that %38 of neuro-sarcoidosis patients are diagnosed with optic nerve involvement, which is characterized by painless progressive vision loss [36, 38–40]. As a result of the dosage increase in steroids which is primarily used for systemic symptoms, a fast clinical response is obtained in both of patients with neuro-sarcoidosis. Subsequently, azathioprine is added to the therapy.

Eye involvement is one of the important findings of sarcoidosis. It may be the initial sign of the disease, or may occur in the course of the disease [6]. Uveitis seen in the course of the disease may occur before systemic findings or in the 1st year of the disease [6]. Ocular involvement may differ by race or country; therefore, the frequency of involvement has been reported to be between 10 and 60% in the literature, which is quite a wide margin [6]. In a study investigating the etiology of uveitis, the rate of sarcoidosis was reported to be 5% [41]. In a study conducted in Turkey, eye involvement rate was 12.9% [6]. In our series, too, eye involvement was prominent as quite a common complaint. A total of 11 (19.60%) patients were diagnosed with uveitis.

It is known that primary rheumatic diseases such as primary Sjögren's syndrome, systemic lupus erythematosus, scleroderma, and ankylosing spondylitis accompany sarcoidosis. Anti-CCP, ANA, and RF positivity can be seen in the course of sarcoidosis, which may cause difficulties in the differential diagnosis [8, 9, 42–45]. In our study, two patients are classified as primary Sjögren's syndrome, while one is diagnosed with ankylosing spondylitis. During sarcoidosis, sacroiliitis may develop, and association with AS may also be seen. It has been reported that sacroiliac joint involvement is seen in 14% of sarcoidosis and is associated with female gender, HLA-B27 negativity and bilateral involvement [24, 44]. Sjögren's syndrome is also important in terms of both differential diagnosis and co-occurrence. Sarcoidosis and Sjögren's syndrome are both chronic inflammatory conditions that can affect the salivary glands and co-occur, although the incidence of coexistence is unknown. Medical history, salivatory gland biopsy, and serological tests, including ANA, SSA, and SSB, are helpful to distinguish these two conditions, and sarcoidosis must be an exclusion to diagnose Sjögren's syndrome [24].

Despite the absence of a specific laboratory test to diagnose sarcoidosis, many changes can be detected during the disease. It has been reported that tests such as RF, ANA, and ANTI-CCP, frequently used in rheumatology practice, may yield findings during sarcoidosis alone, without an overlap syndrome [8, 23, 46]. In our patient group, ESR and CRP values as acute phase reactants were found to be significantly higher in acute sarcoidosis patients. In the outpatient clinic, high CRP and ESR values were found in patients with distinctive arthritis findings, especially polyarticular involvement. CRP and ESR values were also elevated in the patient with parotid involvement. Serum ACE levels can often be expected to be high in patients with chronic arthritis or diffuse sarcoidosis with lung and extrapulmonary involvement [16, 18]. Comorbidities and drugs used may affect serum ACE levels. In our sample, it was remarkable that our patients with high ACE levels had an inadequate response to NSAIDs due to prolonged disease duration and persistent arthritis.

There are many options for sarcoidosis treatment, such as NSAIDs, steroids, methotrexate, azathioprine, hydroxychloroquine, and TNF inhibitors [38, 47, 48]. Many factors, including the extent of the disease, whether it is acute or chronic, and lung involvement can determine the drug to be used in the treatment and the duration [31, 38, 47, 48]. While NSAIDs are usually sufficient in patients with mild symptoms or acute sarcoidosis, some patients may need steroid MTX or azathioprine, depending on the severity of joint findings or organ involvement [47, 48]. Considering the treatment distribution of the patients in our series, it is seen that non-steroidal anti-inflammatory treatments were used in 15 (26.8%) patients, corticosteroids in a total of 40 (71.4%) patients, methotrexate in a total of 15 patients (26.8%), azathioprine in six (10.7%) patients, hydroxychloroquine in 14 (25%) patients, and infliximab in one (1.8%) patient.

Several limitations to the present study warrant attention. The first limitation of our study is the small sample size. The cross-sectional design is another limitation of this study. This study does not provide sufficient results to investigate

treatment responses and temporal variation of the clinical features of the disease. Despite these limitations, our results support the previous findings that sarcoidosis should be kept in mind as a differential diagnosis in patients applying to the rheumatology outpatient clinic, and patients diagnosed with sarcoidosis should be evaluated in detail in terms of systemic involvement.

## Conclusion

While sarcoidosis patients may present to rheumatology outpatient clinics with musculoskeletal complaints or skin findings, they may occasionally be referred from other clinics for a consultation to investigate the etiology of uveitis [47]. As sarcoidosis is a mimicking disease, a good differential diagnosis should be made to avoid misdiagnosis and not be late in diagnosis and treatment. Physicians, especially rheumatologists, should remember sarcoidosis more frequently as the disease may overlap with other rheumatological diseases, rheumatic diagnostic tests may yield positive results in the course of the disease, and rheumatological complaints and findings are detected at the onset or during the disease.

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**Data availability** The authors of current study confirm that the findings of this study are available and resented with the manuscript. All raw data and findings available with corresponding author and can be provided upon request.

## Declarations

**Conflict of interest** The authors have no affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

**Compliance with ethical standards** Current study conducted retrospectively and informed consent was not obtained. Current study approved by the Committee on the Human Research Ethics.

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