



# Sarcoidosis from the Perspective of Rheumatology: Three Years of Experience

## Romatoloji Gözünden Sarkoidoz: Üç Yıllık Deneyim

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### ABSTRACT

**Aim:** The aim of this study is to shed light on sarcoidosis from a rheumatology perspective and to provide a better understanding of sarcoidosis from the perspective of a rheumatologist.

**Materials and Methods:** The files of patients who applied to the rheumatology outpatient clinic with joint complaints between 2020 and 2023 and were diagnosed with sarcoidosis during follow-up or who were already diagnosed with sarcoidosis and had joint complaints during the course of the disease, were retrospectively examined.

**Results:** Joint involvement was observed in all patients (100%). When patients were grouped according to the joints involved, it was found that 17 patients had ankle involvement (60.7%), six patients had metacarpophalangeal joint involvement (21.4%), four (14.2%) patients had wrist involvement, and three (10.7%) patients had knee involvement. Shoulder involvement was detected in one (3.5%) patient.

**Conclusion:** Although sarcoidosis seems to primarily concern chest diseases, from the perspective of rheumatology, it is a very confusing and surprising disease with its heterogeneous nature and joint involvement. It is one of the diseases that should be kept in mind and further studied in rheumatology practice.

**Keywords:** Sarcoidosis, arthritis, joint involvement

### ÖZ

**Amaç:** Bu çalışmanın amacı romatoloji gözüyle sarkoidoz hastalığına ışık tutmak ve romatolog gözüyle sarkoidozun daha iyi anlaşılmasını sağlamaktır.

**Gereç ve Yöntem:** Romatoloji polikliniğine 2020-2023 yılları arasında eklem şikayetleri ile başvurarak izlemde sarkoidoz tanısı almış veya halihazırda sarkoidoz tanısı mevcut olup hastalık seyrinde eklem şikayetleri mevcut olan hastaların dosyaları retrospektif olarak incelendi.

**Bulgular:** Hastaların hepsinde (%100) eklem tutulumu görüldü. Tutulan eklemlere göre hastalar gruplandırıldığında 17 hastada ayak bileği (%60,7) tutulumu, altı hastada metakarpofalangeal (%21,4) eklem tutulumu, dört (%14,2) hastada el bileği tutulumu, üç (%10,7) hastada diz tutulumu, bir (%3,5) hastada omuz tutulumu tespit edildi.

**Sonuç:** Sarkoidoz primer olarak göğüs hastalıklarını ilgilendiriyor gibi görünse de, romatoloji gözünden de heterojen doğası ve eklem tutulumlarıyla oldukça kafa karıştırıcı ve şaşırtıcı bir hastalıktır. Romatoloji pratiğinde akılda tutulması ve üzerinde daha fazla çalışma yapılması gereken hastalıklardan biridir.

**Anahtar Kelimeler:** Sarkoidoz, artrit, eklem tutulumu

## INTRODUCTION

Sarcoidosis is a chronic, multisystemic, and inflammatory disease characterized by non-caseating granulomas, which can manifest throughout the body, with a predilection for the lungs and intrathoracic lymph nodes. Typically observed

in individuals aged 20-40 years, it affects both men and women equally. However, a secondary peak has been observed in women over the age of 50 years. The development of sarcoidosis is believed to involve a combination of genetic predisposition and environmental factors<sup>1</sup>. While it has been demonstrated that infections and occupational factors play

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a role in the development of the disease, the exact cause of sarcoidosis remains unknown<sup>2</sup>. The incidence and prevalence of sarcoidosis exhibit significant variations among different racial groups. In our country, the annual incidence is reported as 4/100,000<sup>3</sup>. The clinical course of sarcoidosis and the affected organs can vary among societies. The first documented case of sarcoidosis in our country dates back to 1953, when Akkaynak reported it, and a comprehensive study by Demirkök et al.<sup>4-6</sup>, involving 275 individuals, described the characteristics of sarcoidosis patients. However, a definitive profile of sarcoidosis patients in our country has not yet been established in the studies conducted thus far.

The organs most commonly affected by sarcoidosis are the lungs and intrathoracic lymph nodes, with an incidence of 90%<sup>7</sup>. Bilateral symmetric lymphadenopathy is frequently observed in the lungs. Following these organs, the skin ranks second in terms of involvement. Sarcoidal granulomas may manifest in the skin, accompanied by reactive, non-specific inflammation clinically presenting as erythema nodosum<sup>8</sup>. In addition to the lungs and skin, other organs such as the liver, spleen, nervous system, kidney, parathyroid glands, heart, and eyes may be affected during the course of the disease. Sarcoidosis can be identified through a routine chest X-ray, or it can involve multiple organs simultaneously. In this multisystemic disease, joints can also be affected, clinically appearing as arthritis. Although sarcoidosis is not commonly associated with acute arthritis, it is estimated that 15-20% of sarcoidosis cases are complicated by arthritis. Sarcoidosis should be considered in the differential diagnosis of ankle joint involvement, especially when respiratory symptoms are also present<sup>9</sup>.

The most commonly reported symptoms in the course of sarcoidosis include cough, shortness of breath, and chest pain<sup>10</sup>. Diagnosis is established by the presence of one or more of the following criteria: radiological signs of sarcoidosis, evidence of systemic involvement, histopathologically proven non-caseating granulomas, demonstration of sarcoidosis findings in bronchoalveolar fluid, and exclusion of other granulomatous diseases. While there is no specific biomarker for the diagnosis of the disease, several markers aid in the diagnostic process, with angiotensin-converting enzyme (ACE) being the most commonly used. Granulomas developing during sarcoidosis can increase ACE activity and stimulate the synthesis of 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub>, resulting in elevated plasma calcium levels. Due to the heterogeneous nature of the disease and variations in its course, diagnosis and treatment planning can pose challenges for clinicians. Despite being generally considered a benign disease with a favorable prognosis, mortality in sarcoidosis, which is observed in 1-5% of cases<sup>11</sup>, is typically attributed to respiratory failure, cardiac involvement, and nervous system

complications. The indications for treatment in this disease remain controversial.

Our study involves a retrospective analysis of patients who visited the rheumatology outpatient clinic between 2020 and 2023 and were diagnosed with sarcoidosis in that clinic. We also included patients diagnosed with sarcoidosis, who presented with the complaints of arthritis or arthralgia. The aim is to provide valuable insights for clinicians dealing with sarcoidosis in rheumatology practice.

## MATERIALS AND METHODS

We conducted a retrospective examination of the medical records of patients who presented to the rheumatology outpatient clinic between 2020 and 2023. This included individuals diagnosed with sarcoidosis during follow-up or those who were already diagnosed with sarcoidosis and experienced joint complaints during the course of the disease. We collected and recorded demographic characteristics, comorbidities, organs involved, joint involvement at the time of diagnosis, medications used during follow-up along with their duration, patients' relapse status, and autoantibodies (rheumatoid factor, citrullinated protein antibodies, and antinuclear antibodies) from the hospital data system and patient files.

### Statistical Analysis

The data were transferred to the Statistical Package for the Social Sciences 27.0 program for evaluation, where descriptive statistics such as frequency, percentage, and average were employed.

## RESULTS

In our study, 28 patients were seen in the rheumatology outpatient clinic during the examined time period. Of these, 21 were female and 7 were male, resulting in a female-to-male ratio of 3. The average age of all patients was 52 years, ranging from a minimum of 39 years to a maximum of 68 years. The average age for female patients was 52.9 years, while it was 49.57 years for male patients. Examining accompanying diseases, 13 patients (46%) had no comorbidities. Two patients (7%) had concomitant hyperthyroidism, three (10%) had hypothyroidism, three (10%) had diabetes mellitus, and seven (25%) had hypertension. Two patients had ankylosing spondylitis and one of them developed sarcoidosis while using biological agents for ankylosing spondylitis. Additionally, two patients had heart failure, two had coronary artery disease, one had ulcerative colitis, and one had vitiligo. When assessing family histories, one of the 28 patients (3.5%) had a positive family history.

In terms of sarcoidosis involvement, joint involvement was observed in all patients (100%). The distribution of joint involvement included 17 patients with ankle involvement (60.7%), six patients with metacarpophalangeal joint involvement (21.4%), four patients with wrist involvement (14.2%), and three patients with knee involvement (10%). One patient (3.5%) had shoulder involvement (Table 1).

In our study focusing on organ involvement in sarcoidosis patients, the examination revealed lung involvement in 24 patients (85.7%), skin involvement in six patients (21.42%), liver involvement in three patients (10.7%), eye involvement in two patients (7.1%), and renal involvement in one patient (3.5%). Among the skin involvement cases, five were identified as erythema nodosum, and one patient exhibited skin involvement without further specification. Lymph node involvement outside the lung was observed in six patients (21.42%), with inguinal lymph node involvement in three of them and axillary lymph node involvement in the remaining three (Table 2).

When considering the years of diagnosis in our study, the longest duration of the disease was found to be 18 years. Two patients were diagnosed in 2023. Regarding diagnostic methods, mediastinoscopy and lymph node biopsy were performed in six patients (21.4%), endobronchial ultrasonography and lymph node biopsy in 14 patients (50%), axillary lymph node biopsy in one patient, inguinal lymph node biopsy in two patients, and skin biopsy in two patients. Additionally, the diagnosis was established through a biopsy in one patient, open lung sampling in one patient, kidney biopsy in one patient, and liver biopsy in one patient.

**Table 1. Our patients according to joint involvements**

	n=%
Ankle	60.7
MCF	21.4
Wrist	14.2
Knee	10.7
Shoulder	3.5

MCF: Metacarpophalangeal

**Table 2. Extrapulmonary region involvement**

Region	n=%
Joint	100
Lung	85.7
Extrapulmonary lymph node	21.4
Skin	21.4
Liver	10.7
Eye	7.1
Kidney	3.5

When examining patients based on their complaints at the time of diagnosis, it was noted that four patients (14.2%) were diagnosed with joint swelling and pain at the rheumatology outpatient clinic. Analyzing the complaints of the remaining twenty-four patients at the time of diagnosis revealed dyspnea in nine patients, erythema nodosum in five patients, left temporal lesion in one patient, anterior uveitis in two patients, and cough in seven patients (25%) (Table 3). Among the patients, 15 (53.5%) were identified as smokers at the time of diagnosis.

Regarding sarcoidosis treatment, 23 patients (82%) received systemic steroids, four were monitored without medication, and one was managed with local steroids. Six patients (21%) were prescribed methotrexate for arthritis accompanying sarcoidosis, and colchicine was used in four patients. In terms of treatment duration, the patient receiving systemic steroids intermittently for nine years experienced disease relapse upon steroid discontinuation.

In terms of laboratory parameters, hypercalcemia was observed in six patients (21.4%). Antinuclear antibody was positive in four patients (14.2%), and rheumatoid factor was positive in one patient (3.5%). The average serum ACE level was 57.96 U/L, with ten patients (35.7%) exceeding the laboratory ACE upper limit of 52 U/L.

**DISCUSSION**

In our study on sarcoidosis patients, 21 were female, and seven were male (F/M=3). The higher number of women aligns with findings from other studies conducted in our country. In a study by Karalezli et al.<sup>12</sup>, the female-to-male ratio was 2.12, and in Aytemur et al.'s<sup>13</sup> study, this ratio was reported as 2.38. The average age of our patients was 52 years, consistent with literature findings. In a study by Fritscher-Ravens et al.<sup>15</sup>, the average age of sarcoidosis patients was 60 years, while in a 2007 study by Miwa et al.<sup>14</sup>, the average age was reported as 50 years. Examining our patients for chronic comorbid diseases, more than half were found to have chronic conditions. This observation may be attributed to the average age of the patients and the fact that they were evaluated in a multidisciplinary chest diseases and rheumatology outpatient clinic.

**Table 3. Extrapulmonary region involvement**

	n=28
Dyspnea	9 (32.1%)
Cough	7 (25%)
Erythema nodosum	5 (17.8%)
Arthritis, arthralgia	4 (14.2%)
Anterior uveitis	2 (7.1%)
Skin lesion	1 (3.57%)

Two of our patients had concurrent ankylosing spondylitis, a rare occurrence reported infrequently in the literature. In one study, three separate cases were examined, and the coexistence of spondyloarthritis and sarcoidosis was considered coincidental<sup>16</sup>. Remarkably, we observed sarcoidosis development in one patient undergoing biological agent treatment (infliximab) for ankylosing spondylitis. Upon the discontinuation of infliximab, we initiated adalimumab for ankylosing spondylitis in this patient and observed that the disease did not progress under adalimumab. Interestingly, the literature also mentions the development of sarcoid uveitis under biological agents, as reported in a multicentric retrospective study of 16 patients conducted by Sobolewska et al.<sup>17</sup> in 2022. Another study, published in June 2023, documented liver sarcoidosis in a patient receiving infliximab for inflammatory bowel disease<sup>18</sup>. Moreover, there is a growing body of research on the use of biological agents for the treatment of sarcoidosis. In our study, only one patient had familial sarcoidosis, aligning with findings from the study by Musellim et al.<sup>3</sup>, where the rate of familial sarcoidosis was 1%. This rate appears consistent with our study and is in line with another study reporting a three percent rate. Considering this, it becomes crucial to inquire about family history in patient practice.

In daily clinical practice, arthritis and joint involvement are often overlooked in the context of sarcoidosis. Literature reports suggest that 15-25% of sarcoidosis patients may experience joint involvement<sup>9</sup>. However, in our study, joint involvement was observed in all patients, which can be attributed to the rheumatology perspective from which the study was conducted. The first joint affected in our study was the ankle, followed by the metacarpophalangeal joint. This is consistent with findings from a study by Sucharita Shanmugam in 2008, where sarcoidosis arthropathy was discussed, with a focus on metacarpophalangeal joint involvement. Similarly, a study by Kiely and Lloyd<sup>19</sup>, published in June 2021, explored ankle arthritis, identifying sarcoidosis as one of the diseases associated with this condition.

The initial complaint in four patients in our study was joint involvement, and further investigation led to the diagnosis of sarcoidosis. Literature reports indicate that joint involvement can be the initial symptom of sarcoidosis, with some patients presenting under a specific subheading known as Löfgren's syndrome. However, in our patient group, only one of these four patients exhibited erythema nodosum during the clinical course, which is a characteristic feature of Löfgren's syndrome.

As a result, joint involvement in sarcoidosis can manifest both during the course of the disease and as its initial symptom. A multidisciplinary approach, involving specialties such as rheumatology, appears appropriate for the comprehensive

follow-up and treatment of this condition, given its heterogeneous nature.

Sarcoidosis is a multisystem disease with the potential to affect various organs. Our study revealed that the most commonly involved organs were the lung and extrapulmonary lymph nodes, with the skin following closely. These findings align with existing literature. In a study conducted in Japan, approximately 20% of patients with systemic sarcoidosis exhibited skin involvement, with erythema nodosum being the most frequently described manifestation<sup>20</sup>. Consistently, our study found a similar rate of skin involvement, with erythema nodosum being the predominant presentation.

In our study, one patient received a diagnosis of sarcoidosis through kidney biopsy. Exploring the literature on the association between sarcoidosis and the kidneys, we found renal involvement to be relatively rare. A case report by Wang et al.<sup>21</sup> highlighted a patient diagnosed with sarcoidosis through a kidney biopsy conducted due to chronic kidney disease. A multicentric retrospective study conducted in Germany in 2023 defined the rate of renal involvement as 27.5% in sarcoidosis patients, emphasizing the significance of not overlooking renal complications in the course of sarcoidosis<sup>22</sup>. Consequently, clinicians should consider sarcoidosis as a potential cause in patients with unexplained chronic renal failure.

In our study, one patient received a diagnosis of sarcoidosis through liver biopsy, revealing liver involvement in 10% of the patients. In a sarcoidosis study conducted in France with 21 patients, liver involvement was observed in seven patients, representing a rate slightly higher than that observed in our study. Another study by Ibrahim et al.<sup>23</sup> suggested that liver involvement in sarcoidosis might vary between 5% and 30%. The rate of liver involvement in our study aligns with the range reported by Ibrahim. In conclusion, it emphasizes the importance of considering the liver as one of the organs that should be taken into account in the course of sarcoidosis.

Sarcoidosis is a systemic granulomatous inflammatory disease known for its frequent ocular involvement. A study in Tunisia reported ocular involvement, specifically in the form of uveitis, in two cases among a sarcoidosis group of 28 patients<sup>24</sup>. Similarly, in our study, two patients exhibited ocular involvement, with anterior uveitis identified upon examination. This underscores the importance of considering sarcoidosis in the etiology of uveitis.

Sarcoidosis may manifest extrapulmonary lymph node involvement during its course. Studies in the literature have reported cases of sarcoidosis exclusively involving cervical and inguinal lymph nodes without lung involvement. Isolated inguinal and axillary lymph node involvement has also been

documented. In our patient group, we observed axillary and inguinal lymph node involvement. Remarkably, 10% of patients in our study received their diagnosis through extrapulmonary lymph node biopsy, underscoring the significance of considering this aspect in the diagnostic process.

In our study, the most prevalent complaints among patients were dyspnea (32.1%) and cough (25%), in consistency with a sarcoidosis study conducted by Ertuğrul et al.<sup>25</sup> in 2008. Similarly, Karalezli et al.'s<sup>12</sup> sarcoidosis study highlighted cough and dyspnea as the most common complaints. These observations align with results from Sharma et al.'s<sup>26</sup> study on 156 sarcoidosis patients in the Indian population. Following dyspnea and cough, the most frequent presenting symptom was erythema nodosum, followed by arthritis. A study by Kiter et al.<sup>27</sup> in our country noted erythema nodosum in 17.1% of patients as a presenting symptom, and in our study, the incidence of erythema nodosum mirrored these findings.

In the sarcoidosis study by Musellim et al.<sup>3</sup>, it was reported that 75% of the patient group consisted of non-smokers, suggesting a potential negative relationship between sarcoidosis and smoking. However, in our study, approximately half of the sarcoidosis patients were identified as smokers, indicating a higher smoking rate compared to other studies in the literature<sup>28-30</sup>. This variance might be attributed to the elevated prevalence of female smokers in our region.

82% of our patients received systemic steroid treatment after diagnosis, indicating a higher rate compared to Ertuğrul et al.'s<sup>25</sup> sarcoidosis study, where systemic steroids were indicated for 52.9% of patients. Literature suggests that spontaneous remissions may occur in about two-thirds of sarcoidosis patients. However, if organ damage develops during the course of the disease, the effectiveness of treatment diminishes<sup>5,31</sup>. Therefore, careful consideration is needed when determining which patients should receive systemic steroids at the time of diagnosis. Typically, systemic steroid treatment in the literature is reported to span around two years<sup>32</sup>. In our study, the duration of steroid administration varied based on the patient's clinical condition, with one patient experiencing relapses in the past and receiving intermittent systemic steroid treatment for nine years. The duration of systemic steroids used in the course of sarcoidosis should be assessed in accordance with the patient's relapses and overall clinical condition.

Hypercalcemia was detected in 21.4% of our patients. Granulomas in sarcoidosis, particularly those secreting cytokines such as interferon- $\gamma$ , stimulate  $1\alpha$  hydroxylase, leading to the production of active vitamin D. This process increases calcium absorption through both intestinal absorption and bone resorption<sup>33</sup>. Comparatively, in a literature study with 1606 patients, the rate of sarcoidosis-related hypercalcemia was reported as 6%<sup>34</sup>. In an American sarcoidosis study with

196 patients, the frequency of hypercalcemia was found to be 18.3%, a rate resembling our study. Meanwhile, a study in Poland reported a 10% occurrence of sarcoidosis-related hypercalcemia. The varying rates across different countries highlight the diverse presentation of sarcoidosis-related hypercalcemia in the literature.

In our sarcoidosis patient group, the examination of ACE levels revealed that 35.7% of the patients had levels exceeding the laboratory upper limit. A study by Sejdıć et al.<sup>35</sup>, involving 101 patients, reported increased serum ACE levels in 48% of the patients, a rate similar to our findings. In a Chinese study, ACE demonstrated a specificity of 93% in diagnosing sarcoidosis, with reports suggesting higher ACE levels in patients with systemic involvement compared to those with simple lung involvement<sup>36</sup>. Notably, our study observed elevated ACE levels, particularly in patients with extrapulmonary organ involvement. In a sarcoidosis study in Tunisia involving 80 patients, serum ACE levels were found to be increased in all patients<sup>37</sup>. However, it is important to note that cut-off values for this enzyme vary in clinical practice across laboratories and countries. Ongoing research in some countries aims to update these cut-off values. In a Japanese study, it was emphasized that normal ACE levels in serum do not easily exclude sarcoidosis, and careful evaluation of this biomarker is necessary. While ACE levels may not be indicative in all cases, the literature underscores its significance, especially in certain sarcoidosis cases with involvement in unusual areas. Ongoing studies, particularly in phenotyping and the diagnostic use of ACE, contribute to the evolving understanding of sarcoidosis.

According to the laboratory results of our sarcoidosis patients, 14.2% showed ANA (antinuclear antibody) positivity, while 3.5% exhibited RF (rheumatoid factor) positivity. The association of these autoantibodies with sarcoidosis has been explored in the literature, although the nature of this relationship remains incompletely understood. A 2023 Japanese study suggested a correlation between autoantibody positivity and the severity of lung involvement<sup>38</sup>. A 2020 study in our country found that RF-positive sarcoidosis patients more frequently experienced hand joint involvement<sup>39</sup>. The literature has also investigated patients with sarcoidosis accompanied by Sjögren's syndrome, revealing ANA positivity in 23 and RF positivity in 12 out of 41 patients. It has been suggested that positive immunological parameters in sarcoidosis patients may indicate more multisystemic involvement<sup>40</sup>. In a study by Yildiz et al.<sup>39</sup> in our country, the relationship between anti-CCP and sarcoidosis was examined, indicating that anti-CCP positivity in sarcoidosis patients is similar to the healthy population, a result consistent with our study. None of our patients tested positive for anti-CCP. The study also found RF positivity in 16% of patients with sarcoidosis. While these findings provide insights, more studies are needed to comprehensively understand the relationship between sarcoidosis and autoantibodies.

## Study Limitations

As our study focused on sarcoidosis from the rheumatology outpatient clinic perspective, all our patients exhibited arthritis during the course of the disease. Consequently, there is a limitation in terms of assessing the frequency of joint involvement. Additionally, given that sarcoidosis cases are typically directed to chest diseases outpatient clinics, our study's patient count is relatively small, and the sample size is limited.

## CONCLUSION

In our study, we examined the demographic characteristics, comorbidities, organs involved, joint involvement at the time of diagnosis, medications used in follow-up, and autoantibodies of 28 sarcoidosis patients diagnosed in the rheumatology outpatient clinic or consulted to the rheumatology outpatient clinic. While sarcoidosis is commonly associated with chest diseases, it presents a perplexing and surprising aspect from the rheumatology perspective due to its heterogeneous nature and joint involvement. Thus, it underscores the importance of considering and further investigating sarcoidosis in rheumatology practice.

## Ethics

**Ethics Committee Approval:** The study was approved by the Tekirdağ Namık Kemal University of Local Ethics Committee (protocol no: 2023.176.10.05, date: 31.10.2023).

**Informed Consent:** Retrospective study.

## Authorship Contributions

Concept: R.M., Design: R.M., Data Collection or Processing: D.B.G., Analysis or Interpretation: D.B.G., Literature Search: D.B.G., Writing: D.B.G.

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

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## REFERENCES

- Iwai K, Sekiguti M, Hosoda Y, DeRemee R, Tazelaar H, Sharma O, et al. Racial difference in cardiac sarcoidosis incidence observed at autopsy. *Sarcoidosis*. 1994;11:26-31.
- Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: Epidemiology and clinical insights. *J Intern Med*. 2023;293:668-80.
- Musellim B, Kumbasar O, Ongen G, Cetinkaya E, Turker H, Uzaslan E, et al. Epidemiological features of Turkish patients with sarcoidosis. *Respir Med*. 2009;103:907-12.
- Gurkan OU, Celik G, Kumbasar O, Kaya A, Alper D. Sarcoidosis in Turkey: 1954-2000. *Ann Saudi Med*. 2004;24:36-9.
- Kumbasar ÖÖ. Sarkoidoz. *Solunum*. 2008.
- Demirkok SS, Basaranoglu M, Akinci ED, Karayel T. Analysis of 275 patients with sarcoidosis over a 38 year period; a single-institution experience. *Respir Med*. 2007;101:1147-54.
- Baughman RP. Pulmonary sarcoidosis. *Clin Chest Med*. 2004;25:521-30.
- Wanat KA, Rosenbach M. Cutaneous sarcoidosis. *Clin Chest Med*. 2015;36:685-702.
- Ogami R, Otsuka Y, Hasegawa K, Tokumasu K, Obika M, Fujii M, et al. Acute arthritis caused by sarcoidosis. *J Gen Fam Med*. 2023.
- Iannuzzi M, Rybicki B, Teirstein AS. Sarcoidosis *N Engl J Med*. 2007;357:2153-65.
- Costabel U, Hunninghake G. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis statement committee. American thoracic society. European respiratory society. World association for sarcoidosis and other granulomatous disorders. *European Respiratory Journal*. 1999;14:735-7.
- Karalezli A, Ünsal M, Gündoğdu C, Dursun G, Başer Y. Sarkoidozlu 50 olgunun değerlendirmesi. *Türkiye Klinikleri Tıp Bilimleri Dergisi*. 1998;18:245-54.
- Aytemur ZA, Erdinç M, Erdinç E, Ateş H, Akyürekli O. Clinical features and diagnostic approach to sarcoidosis according to stages. *Tuberk Toraks*. 2003;51:11-6.
- Miwa S, Suda T, Morita S, Inui N, Sato J, Chida K. Clinical analysis of sarcoidosis presenting with heterochronic cardiac involvement. *Respirology*. 2007;12:744-8.
- Fritscher-Ravens A, Ghanbari A, Topalidis T, Pelling M, Kon O, Patel K, et al. Granulomatous mediastinal adenopathy: can endoscopic ultrasound-guided fine-needle aspiration differentiate between tuberculosis and sarcoidosis? *Endoscopy*. 2011:955-61.
- Kremer P, Gallinet E, Benmansour A, Despau J, Toussiot E, Wendling D. Sarcoidosis and spondylarthropathy. Three case-reports. *Rev Rhum Engl Ed*. 1996;63:405-11.
- Sobolewska B, Baglivo E, Edwards AO, Kramer M, Miserochi E, Palestine AG, et al. Drug-induced sarcoid uveitis with biologics. *Ocul Immunol Inflamm*. 2022;30:907-14.
- Chebli JMF, Evangelista RKA, Chebli LA. Persistent Constitutional Symptoms and Cholestasis During Anti-TNF Therapy as a Harbinger of a Surprising Condition. *Gastroenterology*. 2023.
- Kiely PDW, Lloyd ME. Ankle arthritis - an important signpost in rheumatologic practice. *Rheumatology (Oxford)*. 2021;60:23-33.
- Suga Y, Ogawa H. Sarcoidosis of the skin. *Nihon Rinsho*. 1994;52:1603-7.
- Wang Y, Du F, Zhou H. Renal sarcoidosis presenting with chronic kidney disease and hypercalcemia. *Clin Nephrol*. 2023;100:177-80.
- Bergner R, Weiner SM, Kehl G, de Groot K, Tielke S, Asendorf T, et al. Renal disease in sarcoidosis patients in a German multicentric retrospective cohort study. *Respiratory Medicine*. 2023;209:107121.
- Ibrahim AM, Bhandari B, Soriano PK, Quader Z, Gao JZ, Shuster D, et al. Hepatic involvement in systemic sarcoidosis. *Am J Case Rep*. 2018;19:1212-5.
- Benmously R, Chaâbane S, Fenniche S, Marrak H, Mohammed Z, Mokhtar I. Cutaneous sarcoidosis through a hospital series of 28 cases. *Tunis Med*. 2008;86:447-50.
- Ertuğrul A, Tozkoparan E, Balkan A. Sarkoidozlu hasta sonuçlarımız. *Gülhane Tıp Derg*. 2008;50:253-6.
- Sharma SK, Soneja M, Sharma A, Sharma MC, Hari S. Rare manifestations of sarcoidosis in modern era of new diagnostic tools. *Indian J Med Res*. 2012;135:621-9.
- Kiter G, Musellim B, Çetinkaya E, Türker H, Kunt Uzaslan A, Yentürk E, et al. Clinical presentations and diagnostic work-up in sarcoidosis: A series of Turkish cases (clinics and diagnosis of sarcoidosis) Sarkoidozlu olgularda klinik görünüm ve tanısal yaklaşım: Türk olgu serisi (sarkoidoz kliniği ve tanı yaklaşımları). *Tuberkuloz ve Toraks*. 2011;59:248-58.

28. Terris M, Chaves AD. An epidemiologic study of sarcoidosis. *American Review of Respiratory Disease*. 1966;94:50-5.
29. Harf R, Ethevenaux C, Gleize J, Perrin-Fayolle M, Guerin J, Ollagnier C. Reduced Prevalence of Smokers in Sarcoidosis: Results of a Case-Control Study. *Ann N Y Acad Sci*. 1986;465:625-31.
30. Douglas JG, Middleton WG, Gaddie J, Petrie GR, Choo-Kang Y, Prescott RJ, et al. Sarcoidosis: a disorder commoner in non-smokers? *Thorax*. 1986;41:787-91.
31. Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis. *Orphanet J Rare Dis*. 2007;2:46.
32. Grutters J, Van den Bosch J. Corticosteroid treatment in sarcoidosis. *Eur Respir J*. 2006;28:627-36.
33. Reichel H, Koeffler HP, Bishop JE, Norman AW. 25-Hydroxyvitamin D3 metabolism by lipopolysaccharide-stimulated normal human macrophages. *J Clin Endocrinol Metab*. 1987;64:1-9.
34. Baughman R, Janovcik J, Ray M, Sweiss N, Lower E. Calcium and vitamin D metabolism in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2013;30:113-20.
35. Sejdic A, Graudal N, Baslund B. Clinical and biochemical presentation of sarcoidosis with high and normal serum angiotensin-converting enzyme. *Scand J Rheumatol*. 2018;47:487-90.
36. Wang W, Ma Y, Zhang Y, Lin J, He J, Nong Y, et al. Diagnostic and Staging Value of Serum Angiotensin-Converting Enzyme in Sarcoidosis. *Comput Math Methods Med*. 2022;22:2022:4657502.
37. Chebbi D, Marzouk S, Snoussi M, Jallouli M, Gouiaa N, Boudawara T, et al. Retrospective study of elderly onset sarcoidosis in Tunisian patients. *Sarcoidosis Vasc Diffuse Lung Dis*. 2021;38:e2021016.
38. Kawabata H, Satoh M, Hasegawa T, Tanaka S, Hara K, Yatera K. Clinical significance of serum autoantibodies in patients with sarcoidosis. *Immunopharmacol Immunotoxicol*. 2023;45:479-84.
39. Yildiz F, Kobak Ş, Semiz H, Orman M. Concomitant autoimmune diseases in patients with sarcoidosis in Turkey. *Arch Rheumatol*. 2020;8;35:259-63.
40. Song X, Huang H, Liu Y, Zhao Y, Li S, Xu Z. Coexistence of sarcoidosis and primary Sjögren syndrome: A clinical analysis and literature review. *Zhonghua nei ke za zhi*. 2017;56:375-7.