

## Concomitant Autoimmune Diseases in Patients With Sarcoidosis in Turkey

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### ABSTRACT

**Objectives:** This study aims to determine the frequency and characteristics of autoimmune diseases associated with sarcoidosis patients.

**Patients and methods:** The study included 131 sarcoidosis patients (36 males, 95 females; mean age 46.1 years; range, 20 to 82 years). Demographic, clinical, laboratory and radiological data of patients were evaluated retrospectively. The characteristics of autoimmune diseases associated with sarcoidosis (sarcoidosis-overlap group) patients and isolated sarcoidosis (isolated sarcoidosis group) were analyzed and compared.

**Results:** Concomitant autoimmune diseases were detected in 15 (11.5%) (5 males, 10 females; mean age 50.8 years; range, 26 to 58 years) of the 131 patients with sarcoidosis and their mean disease duration was three months (range, 1 to 30 months). When compared with isolated sarcoidosis patients, more hand finger joint involvement, rheumatoid factor (RF) positivity, higher erythrocyte sedimentation rate (ESR) and less nonsteroidal anti-inflammatory drugs (NSAIDs) usage were found in the sarcoidosis-overlap group ( $p=0.035$ ,  $p=0.049$ ,  $p=0.015$ ,  $p=0.018$ , respectively). There were no statistically significant differences between the two groups when evaluated for demographic, clinical parameters and disease-modifying antirheumatic drugs usage.

**Conclusion:** Concomitant autoimmune diseases in patients with sarcoidosis may be rarely seen. These patients are characterized with more hand finger joint involvement, RF positivity, higher ESR and less NSAIDs usage. Multicenter, prospective studies involving large numbers of patients are needed to understand whether the association of sarcoidosis-autoimmune diseases is based only on coincidence or on a common etiopathogenesis.

**Keywords:** Autoimmune diseases, concomitant, sarcoidosis.

Sarcoidosis is a systemic inflammatory disease of unknown etiology that is characterized by the presence of non-caseating granulomas in affected tissues.<sup>1</sup> The immunopathogenesis of sarcoidosis is complex and not completely understood. It is postulated that exposure to an unknown environmental antigen in a predisposed individual leads to an abnormal type I immune response. Sarcoidosis may present with different clinical findings such as lung, skin and eyes involvement. It may mimic some manifestations

of a number of autoimmune diseases and/or develop concomitantly with them.<sup>2</sup> Sarcoidosis may coexist with different rheumatic autoimmune diseases. Some authors have suggested that concurrent disease is rare and may be due to a nonspecific granulomatous reaction and is not truly sarcoidosis. There are also studies reporting that sarcoidosis may aggravate or mimic the clinical and laboratory findings of these diseases.<sup>3</sup> Sarcoidosis does not meet the criteria for autoimmune disease. However, many

**Received:** May 30, 2019 **Accepted:** August 29, 2019 **Published online:** January 08, 2020

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### Citation:

Yıldız F, Kobak Ş, Semiz H, Orman M. Concomitant Autoimmune Diseases in Patients With Sarcoidosis in Turkey. Arch Rheumatol 2020;35(x):i-v.

case reports have suggested that there is an association between various autoimmune diseases and sarcoidosis.<sup>4</sup> To our knowledge, although no data exist of such an association yet, given their prevalence, it is extremely unlikely for patients to develop both diseases concomitantly.

In this study, we aimed to determine the frequency and characteristics of autoimmune diseases associated with sarcoidosis patients.

## PATIENTS AND METHODS

One hundred and thirty-one sarcoidosis patients (36 males, 95 females; mean age 46.1 years; range, 20 to 82 years) followed-up by Şifa University Rheumatology Clinic between January 2012 and May 2016 were retrospectively evaluated. Patients' data were collected and documented using our computer system. Biochemical, serological, laboratory tests and imaging techniques were used for diagnosis. Biopsy specimens taken from different tissues (lymph nodes, skin, parotid gland, penis) were used for histological verification of sarcoidosis, and diagnosis was confirmed as the pathologists showed the non-caseating granulomas. The diagnosis of sarcoidosis was established according to histopathologic, clinical, radiologic, and

laboratory investigations. Other possible causes of granulomatous diseases (tuberculosis, bacterial, fungal infections) were excluded. Laboratory investigations were performed on all patients, and their routine biochemistry, acute phase reactants, serum angiotensin converting enzyme, calcium and hydroxy-vitamin D3 levels were checked. Plain chest radiography and thorax computed tomography (CT) were performed for staging of sarcoidosis. Diagnosis of concomitant autoimmune disease was established according to the diagnostic criteria of the involved diseases. Clinical, demographical, laboratory, radiological and histological data of both groups (sarcoidosis-overlap and isolated sarcoidosis groups) of patients were compiled and analyzed. The study protocol was approved by the Şifa University Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Statistical analysis

Data were analyzed by the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Cross tables were used in analysis of data and Chi-square and Fisher's exact tests were performed where appropriate. The data were given as frequency and percentage. Statistical significance threshold was considered as 0.05.

**Table 1.** Clinical characteristics of sarcoidosis-overlap cohort (n=15)

	n	%	Mean
Sex			
Male	5	33.3	
Female	10	66.6	
Mean age (years)			50.8
Mean disease duration (months)	3		
Race			
Caucasian			
Concomitant autoimmune disease			
Ankylosing spondylitis	4	26.6	
Rheumatoid arthritis	3	20	
Scleroderma	1	6.6	
Sjögren's syndrome	1	6.6	
Familial Mediterranean fever	1	6.6	
Still's disease	1	6.6	
Gouty arthritis	1	6.6	
Graves' disease	1	6.6	
Hashimoto thyroiditis	1	6.6	
Immune thrombocytopenic purpura	1	6.6	

## RESULTS

We identified 15 patients (11.5%) (5 males, 10 females; mean age 50.8 years; range, 26 to 58 years) with concomitant autoimmune disease and sarcoidosis and their mean disease duration was three months (range, 1 to 30 months). The most frequent concomitant autoimmune diseases were ankylosing spondylitis (AS) and rheumatoid arthritis (RA), whereas other patients were diagnosed as Sjögren's syndrome, scleroderma, gouty arthritis, immune thrombocytopenic purpura, Hashimoto thyroiditis and Graves' disease, respectively. Two patients had autoinflammatory diseases (Still's disease and familial Mediterranean fever [FMF]) (Table 1). Sarcoidosis presented

prior to the autoimmune disease in four of 15 patients (26.7%). An autoimmune disease presented prior to sarcoidosis in 9 of 15 patients (60%). Both diseases presented concomitantly in two patients (13.3%). An evaluation of our cohort of 131 sarcoidosis patients for system and organ involvement showed erythema nodosum in 59 patients (45%), uveitis in 18 patients (13.7%), and bone involvement, lupus pernio myositis and neurosarcoidosis in one patient (0.76%). Plain chest radiography and thorax CT results showed stage 0 (extrapulmonary) disease in five patients (3.8%), stage 1 (bilateral hilar lymphadenopathy) in 64 patients (48.8%), stage 2 (bilateral hilar lymphadenopathy + pulmonary infiltrate) in 45 patients (34.3%), stage 3 (only pulmonary

**Table 2.** Comparison between sarcoidosis-overlap and isolated sarcoidosis patients according to demographic, clinical and laboratory features (n=131)

Features	Sarcoidosis-overlap group (n=15)			Isolated sarcoidosis group (n=116)			p
	n	%	Mean	n	%	Mean	
Age (years)			50.8			48.5	0.588
Sex							0.538
Female	10	66.7		86	89.6		
Disease duration (month)			3			12	0.409
Arthralgia	15	100		102	87.9		0.368
Fatigue	8	53.3		69	59.5		0.649
Arthritis	11	73.3		66	56.9		0.224
Hand joints involvement	2	13.3		1	0.9		0.035
Neurosarcoidosis	1	6.7		0	0		0.115
Erythema nodosum	6	40		53	45.7		0.677
Lupus pernio	0	0		1	0.9		1.000
Löfgren syndrome	2	13.3		17	14.7		1.000
Myopathy	0	0		1	0.9		1.000
Uveitis	4	26.7		14	12.1		0.128
Bone involvement	0	0		1	0.9		1.000
Elevated serum ACE	8	53.3		51	44		0.493
Elevated serum ESR	12	80		54	46.6		0.015
Elevated serum CRP	7	46.7		51	44		0.843
RF positivity	4	26.7		11	9.5		0.041
CS use	7	46.7		37	31.9		0.254
NSAIDs use	3	20		61	52.6		0.018
HQ use	3	20		12	10.3		0.379
MTX use	1	6.7		2	1.7		0.308
AZA use	1	6.7		0	0		0.115
CD use	1	6.7		3	2.6		0.389

ACE: Angiotensin converting enzyme; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RF: Rheumatoid factor; CS: Corticosteroids; NSAIDs: Nonsteroidal anti-inflammatory drugs; HQ: Hydroxychloroquine; MTX: Methotrexate; AZA: Azathioprine; CD: Colchicum-Dispert.

infiltrate without hilar lymphadenopathy) in seven patients (5.3%), and stage 4 (pulmonary fibrosis) in 10 patients (7.6%) with sarcoidosis. Histopathological verification of sarcoidosis was performed by endobronchial ultrasound and mediastinoscopy and also by demonstrating non-caseating granulomas through biopsies of the skin, axillary lymphadenopathy, penile mass and parotid gland. Biopsy was not taken in patients presenting with typical clinical features of Löfgren syndrome (fever, bilateral hilar lymphadenopathy, erythema nodosum, ankle arthralgia/arthritis). All 15 sarcoidosis-overlap patients had biopsy-proven diagnosis. Table 2 shows the clinical features of sarcoidosis-overlap and isolated sarcoidosis groups. When compared with isolated sarcoidosis patients, more hand finger joint involvement, rheumatoid factor (RF) positivity, higher erythrocyte sedimentation rate and less nonsteroidal anti-inflammatory drugs usage were found in sarcoidosis-overlap group ( $p=0.035$ ,  $p=0.049$ ,  $p=0.015$ ,  $p=0.018$ , respectively). Arthritis, uveitis and neurosarcoidosis were more common in sarcoidosis-overlap group, but this was not statistically significant. There were no statistically significant differences between both groups when evaluated for demographic, clinical parameters and disease-modifying antirheumatic drugs usage.

## DISCUSSION

Our study showed close association between sarcoidosis and autoimmune diseases. The most frequent concomitant autoimmune diseases were AS and RA. To our knowledge, there are various case reports and only two studies in the literature showing the association of sarcoidosis and AS. A hospital-based study showed higher prevalence of radiological sacroiliitis in patients with sarcoidosis (6.6%) compared with the prevalence of spondyloarthritis (1.9%) in the normal population.<sup>5</sup> These results and the possible association were further supported by our previous study where sacroiliitis was noticed in 14.3% of sarcoidosis patients in Turkey.<sup>6</sup> However, these studies have still not answered the main question of whether there is a true association or incidental coexistence between sarcoidosis and AS. Probably, both diseases share common pathogenic mechanisms, particularly in terms of some pro-inflammatory

cytokines. This hypothesis was partly supported by successful treatment of AS and pulmonary sarcoidosis by infliximab. Sarcoidosis may mimic or coexist with RA.<sup>7</sup> Furthermore, RF and anti-nuclear antibody positivity were reported in patients with sarcoidosis.<sup>8</sup> In a study, the rate of anti-cyclic citrullinated peptide antibodies was determined as 4.7% in patients with sarcoidosis.<sup>9</sup> These antibodies may be important in the differential diagnosis of sarcoidosis-RA overlap syndrome and RA. In our study, we found three sarcoidosis patients with concomitant RA, and this was in accordance with previous cases reported in the literature.<sup>7</sup> Numerous case reports are available on coexistence of sarcoidosis and primary Sjögren's syndrome.<sup>10</sup> Sicca symptoms and parotid gland enlargement may also be present in patients with sarcoidosis. Exocrine gland biopsy, serologic tests, and clinical findings should be taken into consideration in order to differentiate both diseases. Positive serologic tests (anti-Sjögren's syndrome A [anti-Ro] and anti-Sjögren's syndrome B [anti-La] antibodies) support Sjögren's syndrome while the presence of uveitis supports sarcoidosis. Clinical features of both diseases are very similar. Judson et al.<sup>11</sup> reported concomitant sarcoidosis and connective tissue diseases (CTD) in 15 patients followed-up at two medical centers. The patients were predominantly females and scleroderma was the most common CTD. As we report in this study, coexistence of sarcoidosis with gouty arthritis, Still's disease and FMF is rather rare. The relationship between gouty arthritis and sarcoidosis was reported years ago.<sup>12</sup> Because hyperuricemia and similar clinical pictures may occur in both diseases, demonstration of monosodium urate crystals phagocytosed by neutrophils is diagnostic for gouty arthritis. Autoimmune thyroid diseases are the most frequently reported autoimmune comorbidities associated with sarcoidosis. In a case-control study including 111 cases of sarcoidosis, a higher prevalence of clinical hypothyroidism (5.3%) and Graves' disease (4.0%) was reported in female patients with sarcoidosis compared with age- and sex-matched controls.<sup>13</sup> In addition, a higher prevalence of Hashimoto thyroiditis (11%) in pulmonary sarcoidosis patients, and significant association between thyrotoxicosis and sarcoidosis were reported.<sup>14,15</sup> In our study, we detected two patients with thyroid autoimmune diseases coexisting with sarcoidosis.

Our study has some limitations. The restricted data from only one center and relatively small number of patients would not allow us to generalize our results. Moreover, since the clinical presentations of sarcoidosis may vary with respect to ethnicity, the results of the current study might not be generalizable to other populations.

In conclusion, our study showed the association of sarcoidosis with some autoimmune diseases in Turkey. The study demonstrated that sarcoidosis patients were more likely associated with AS, RA and autoimmune thyroid disease. We advise physicians to be alert against autoimmune comorbidities in sarcoidosis patients to ensure early diagnosis and treatment. More prospective studies are needed in this regard.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### Funding

The authors received no financial support for the research and/or authorship of this article.

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