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How much are we aware of the increase in accompanying comorbidities in sarcoidosis?

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Abstract:

OBJECTIVE: Sarcoidosis is a multisystem chronic disease characterized by granulomatous inflammation. It is reported that the frequency of other inflammatory and malignant diseases increases. The primary objective of the study is to determine the types of comorbid diseases and their frequency, and whether the risk of malignancies and autoimmune diseases such as rheumatoid arthritis and thyroid increases. The secondary objective is to identify the factors related to the comorbidities frequently detected.

METHODS: The files of 694 patients who had the diagnosis of sarcoidosis between1998-2016 were evaluated. The frequency of comorbid diseases recorded was compared to the data of our country.

RESULTS: Among the patients, 487 (70%) were female, and the mean age at diagnosis was 42.9 ± 11.8 (18-87). In 490 patients (70%) at least one comorbidity was detected. The most frequently detected comorbidities were systemic hypertension (22%), hepatosteatosis (16.9%), diabetes mellitus (16.4%), thyroid diseases (13.1%), and asthma (12%). Malignancy was found in a ratio of 4.0%, rheumatoid arthritis in 2.2%. The comparison to the frequencies across the country showed that the prevalence of diabetes mellitus, thyroid diseases, asthma, malignancy, and rheumatoid arthritis was higher. Diabetes, thyroid diseases, asthma were more frequent in women. The mean age of patients in which diabetes, thyroid diseases, asthma, rheumatoid arthritis or malignancy was detected as a comorbidity was higher than those without comorbidities.

CONCLUSION: Comorbidities frequently occur among sarcoidosis patients, and the frequency of diabetes mellitus, thyroid diseases, asthma, malignancy, and rheumatoid arthritis is higher than the data of the country.

Keywords:

Comorbidity, malignancy, sarcoidosis

Introduction

Sarcoidosis is a multisystem chronic disease characterized by noncaseating granulomatous inflammation. Various infectious and environmental agents, ethnicity, geographical differences, and individual genetic tendency together with an impaired immune system are held responsible in its etiology. All organs may be involved, but lungs and/or intrathoracic lymph nodes are the most commonly affected. Although it is generally known as a self-limiting disease with a favorable course, it may also run a severe trajectory with relapses and multiorgan involvement. Its frequency increases under 40 years of age, particularly among adults from 20 to 29 years of age.[1] While the predicted prevalence of sarcoidosis ranges from 1 to 40 cases in 100,000, the highest incidence is in Nordic countries at 60/100,000.[2] The predicted incidence reported in Turkey is 4/100,000.[3]

Although the immunopathogenesis of sarcoidosis has not been explained

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completely, it has been shown that it is partly autoimmune.[4] By means of antigenic stimulation of unknown etiology, T helper-1 lymphocyte cells (Th1-Ly) and pro-inflammatory cytokines from macrophages (tumor necrosis factor-α [TNF-α], interferon (IFN)-γ, etc.) are stimulated.[1,5] By means of the effects of all the mediators, the main pathological finding of sarcoidosis, which is granulomatous inflammation, develops. While CD4 T-Ly released from Th1-Ly is typically found in granulation tissue, CD8 T-Ly, B-cells, plasma, and mast cells are found less commonly. Th 17 is a mediator from CD4 T-Ly and has an important role in the development of many autoimmune chronic inflammatory diseases that are pathological. In sarcoidosis patients, it has been shown that Th 17 cytokines are increased in the peripheral blood, sarcoid tissue, and granuloma. It has an important role in the progression of the disease.[6]

Th1/Th17 cytokines take part in the development of collagen tissue diseases such as rheumatoid arthritis (RA), Sjögren's syndrome, and spondyloarthropathy.[7] In a similar manner, TNF-α and IFN-γ are also released from Th1-Ly in the thyroid cells in autoimmune thyroid diseases.[8] It has been proposed that all these immunological mechanisms trigger the development of autoimmune thyroiditis and collagen tissue diseases in sarcoidosis patients.

It has been said that chronic inflammation poses a risk for malignancy in sarcoidosis patients, but a complete consensus was failed to be reached.[9-11] Many studies on this subject have been reported in international studies. However, there are no extensive case series in our country.

The primary objective of our study is to identify comorbid diseases in sarcoidosis patients, in particular, chronic inflammatory diseases, and to compare the frequency of malignancy to the data of our country population. The secondary objective is to investigate the determinants related to the comorbid diseases detected in sarcoidosis.

Methods

This is a single-center retrospective cohort study. Patients followed up by the chest diseases training and research hospital's sarcoidosis clinic were included in the study. In our hospital, patients diagnosed with sarcoidosis were enrolled in a routine follow-up program with a follow-up file prepared by the sarcoidosis polyclinic.

In all patients diagnosed, the angiotensin-converting enzyme (ACE) and serum calcium levels (Ca) were assessed, and respiratory function tests, carbon monoxide diffusion capacity evaluation, whole abdominal ultrasonography (USG), electrocardiography, and, depending on symptoms, other organ examinations were performed.

Patient selection

The study included patients followed up in the sarcoidosis polyclinic between September 1998 and September 2016 that met the diagnostic criteria for sarcoidosis, attended routine polyclinic follow-ups, and had all the data required in their medical files.

The diagnostic criteria for sarcoidosis are as follows:

1. Histopathologically, the identification of granulomatous inflammation without necrosis in biopsy samples obtained from the lungs and other organs and ruling out other diseases that cause granulomatous inflammation
2. Patients with clinicoradiological findings consistent with sarcoidosis and those diagnosed with Löfgren syndrome (bilateral hilar lymphadenopathy [BHL], polyarthritis, uveitis, fever, and erythema nodosum) and Heerfordt syndrome (uveitis, bilateral parotitis, frequently fever, and facial nerve paralysis)
3. If biopsy was rejected by the patient or if it was unable to perform a biopsy, patients with bronchoalveolar fluid with lymphocytic characteristics and CD4/CD8 >3.5 with a clinical condition consistent with sarcoidosis.

Exclusion criteria

1. Patients with insufficient data at the time of diagnosis in their medical files (n = 87)
2. Those that dropped out of polyclinic follow-ups (n = 76)
3. Patients in which sarcoidosis was ruled out and diagnosed as nonsarcoidosis (n = 2) and patients in which nonnecrotizing granulomatous inflammation was detected by mediastinoscopy and endobronchial USG but was found out to be lung cancer in follow-ups [Figure 1].

Data collection

Patients' demographic data, diagnostic dates, diagnostic methods, radiological stage at diagnosis, serum calcium

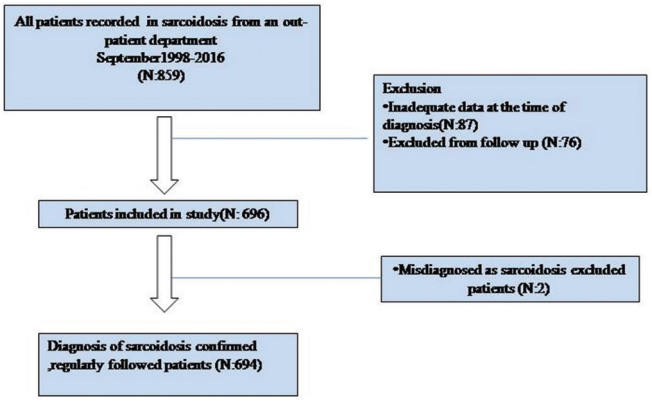

Figure 1: Flowchart of the patients

and ACE levels, and extrapulmonary organ involvement were recorded. The follow-up durations and treatments applied throughout the follow-up were evaluated.

The disease stage was assessed in five stages according to the lung X-ray at diagnosis. Stage 0 reflects a normal lung X-ray, Stage 1 BHL, Stage 2 BHL together with pulmonary infiltration, Stage 3 pulmonary infiltration alone, and Stage 4 reflects a pulmonary fibrosis.[12]

Comorbidity defines one or more diseases that accompany sarcoidosis. Comorbidities were evaluated based on patient files and the electronic database information of the hospital. Diseases that were present before the diagnosis of sarcoidosis, concurrent diseases, and diseases that developed during follow-up were recorded. Chronic diseases and regular medications of all patients were investigated by reviewing the website of the Social Security Institution that is in service in our country since 2010.

Comorbid diseases

Patients' comorbid diseases were diagnosed by doctors who are specialists in their fields by means of physical examination, laboratory tests (T3, T4, thyroid-stimulating hormone, etc.), and imaging (USG, thoracic computed tomography, etc.) techniques.

Study design

Using the data recorded, the frequency of comorbid diseases was investigated. The frequency of additional diseases was compared to the rates presented in the burden of chronic diseases report of the Ministry of Health of 2013.[13] Since the frequency of thyroid diseases was not stated in this report, a separate report from the Ministry of Health was used for thyroid diseases.[14] The relationship between frequently detected comorbid diseases, demographic characteristics, and basal laboratory and radiological features was researched.

Approval for the study was obtained from the hospital's ethical board (No: 11).

Statistical analysis

The study groups were compared if continuous variables (e.g., age and biochemical values) were distributed normally. Student's *t*-test was used and values were specified as mean and standard deviation. Dichotomous variables (e.g., gender, stages of sarcoidosis, and presence of comorbidity) of groups were analyzed by Chi-square test and values were shown as count (%). All statistical analyses were conducted using a statistical software package (SPSS for Windows, version 16.0; SPSS Inc.; Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Of the 694 patients included in the study, 487 (70%) were female, and the mean age was 42.9 years (18–87 years). The most common methods of diagnosis were mediastinoscopy (41.3%), clinicoradiological features (17.2%), and transbronchial biopsy (10.9%). The radiologic staging was most frequently consistent with Stage 1 (58.5%) and Stage 2 (35.1%). Extrapulmonary organ involvement was recorded in 25% of the patients. Among the patients, 28% had received treatment. Median year of follow-up of patients was 2 years (1–23 years). The general characteristics of the patients are presented in Table 1.

Comorbid diseases

At least one comorbid disease was recorded in 70% (n = 490) of all patients. The most frequently occurring diseases are systemic hypertension (n = 153, 22%), hepatosteatosis (n = 117, 17%), diabetes mellitus (n = 114, 16%), thyroid diseases (n = 91, 13%), and asthma (n = 83, 12%) in that order. The rate of hepatomegaly that did not cause organ dysfunction was 9.1% and splenomegaly was 8.6%. Malignancy was detected in 28 (4%) patients. Collagen tissue diseases were recorded in 21 patients, with the most frequent being RA (n = 15) [Table 2].

According to the data of our country's burden of chronic diseases report, the prevalence of systemic hypertension is 24%, hepatosteatosis is 20%, diabetes is 10%, and thyroid diseases is 3.4%.[13,14] It was observed that the frequency of hypertension and hepatosteatosis in sarcoidosis patients was similar to that of the general population of the country, whereas, diabetes mellitus, asthma, malignancy, and RA were more frequent among sarcoidosis patients [Figure 2]. The relationship between the frequency of comorbid diseases and the age, gender, disease stage, serum ACE and Ca levels, and extrapulmonary organ involvement was investigated [Tables 3-6].

The comparison of patients accompanied with and without diabetes mellitus showed that the patients accompanied with diabetes mellitus were older (49.4 vs. 41.7, respectively) ($P < 0.001$) and that diabetes mellitus was more common among female patients (19% vs. 12%, respectively) ($P = 0.025$). The mean age of the patients with thyroid disease was higher (47.6 years vs. 42.2 years, respectively) and the female sex ratio was higher in this group ($P < 0.001$). The female sex ratio (90% vs. 67%, respectively) ($P < 0.001$) and the mean age of the patients were significantly higher (46.4 years vs. 42.4 years, respectively) in sarcoidosis patients with asthma (n = 83) compared to those without asthma. Among the 21 patients in which collagen tissue diseases were detected, 15 had RA. When the patients with and

Table 1: Patients' characteristics (*n*=694)

	n (%)
Gender	
Male	207 (30)
Female	487 (70)
Age, median (range)	42.9 (18-7)
Radiological stage at diagnosis	
Stage 0 (extrapulmonary involvement only)	15 (2.2)
Stage I	406 (58.5)
Stage II	243 (35)
Stage III	26 (3.7)
Stage IV	4 (0.6)
Diagnostic procedure	
Mediastinoscopy	286 (41.2)
Clinicoradiological features	120 (17.2)
TLB	77 (11.1)
Bronchial mucosal biopsy	60 (8.6)
EBUS	48 (7)
Skin biopsy	32 (4.6)
Skin biopsy and other tissue biopsy	27 (3.9)
Thoracoscopic lung biopsy (wedge)	18 (2.6)
Superficial lymph node biopsy	12 (1.7)
Superficial lymph node biopsy and other biopsy	4 (0.6)
TBNA	4 (0.6)
Parotid biopsy	2 (0.3)
Other tissue biopsy (liver, gallbladder)	2 (0.3)
Pleural biopsy	1 (0.1)
Eye biopsy	1 (0.1)
Extrapulmonary involvement	175 (25.3)
Treatment of sarcoidosis	196 (28)
Prednisone	174
Prednisone + second line*	22

*Methotrexate, azathioprine, cyclophosphamide, hydroxychloroquine. TLB: Transbronchial lung biopsy, EBUS: Endobronchial ultrasound, TBNA: Transbronchial needle aspiration

without any collagen tissue disease were compared, it was observed that the mean age of patients was higher in collagen tissue disease (47 vs. 43) and the frequency of female gender was higher ($P < 0.007$) [Table 4].

While the mean age of patients with malignancy was higher than that of the patients without malignancy (49 vs. 43), gender, stage of sarcoidosis, and extra organ involvement were similar across the two groups [Table 5]. The most frequently detected malignancies were gynecological (endometrium cancer in 4, ovarian in 2, and cervical in one patient). Lung cancer was seen in six and thyroid malignancy in four patients. Except for one patient with ovarian cancer, all patients were under 65 years of age. While malignancy was diagnosed after the diagnosis of sarcoidosis in most patients, in six patients, it was diagnosed before sarcoidosis and simultaneously in four patients [Figure 3]. The benign tumors detected in the patients were tubular adenoma of the colon in one patient, pituitary adenoma in one patient, and intracranial myxopapillary ependymoma in one patient.

Table 2: Comorbid diseases and incidence in 694 sarcoidosis patients

Comorbidities	*n* (%)
Systemic hypertension	153 (22)
Hepatosteatosis	117 (17)
Diabetes mellitus	114 (16)
Thyroid disorders	91 (13)
Asthma	83 (12)
Anemia	47 (6.8)
Depression/anxiety	41 (5.9)
Malignancy	28 (4)
COPD	33 (4.8)
Coronary heart disease	31 (4.5)
Gynecological diseases	27 (3.9)
Gastric/duodenal ulcer	23 (3.3)
Kıdney stone, chronic renal disease	23 (3.3)
Cholelithiasis	21 (3)
Osteomalacia	16 (2.3)
Rheumatoid arthritis	15 (2.2)
Allergic rhinitis	13 (1.9)
Arrhythmia	11 (1.6)
Diseases of the nervous system (cerebrovascular accident, epilepsy)	11 (1.6)
Deep-vein thrombosis, pulmonary embolism	10 (1.4)
Migraine	9 (1.3)
Hemangioma	8 (1.2)
Pulmonary hypertension	7 (1)
Carpal tunnel syndrome	6
Other connective tissue diseases*	6
Lichen planus	5
OSAS	5
Psoriasis	5
Parathyroid disease	3
FMF	3
Portal hypertension	2
Vitiligo	2
Others**	7

*Two patients with ankylosing spondylitis, one patient with nodular vasculitis, one patient with seronegative spondyloarthropathy, one patient with antiphospholipid syndrome, one patient with Behcet's disease, **One patient with hemosiderosis, Guillain–Barré syndrome, celiac disease, idiopathic thrombocytopenic purpura, thrombocytopenia, pancytopenia, primary biliary cirrhosis. COPD: Chronic obstructive pulmonary disease, OSAS: Obstructive sleep apnea syndrome, FMF: Familial Mediterranean fever

Discussion

Our study is the first and most extensive study that investigates comorbid diseases in sarcoidosis in our country. In our series, comorbid diseases were detected in most of the sarcoidosis patients (70%). The most common ones among these are hypertension, hepatosteatosis, diabetes, thyroid diseases, and asthma. It was identified that, independent from cortisone treatment in sarcoidosis, the rate of diagnosis with diabetes was high. When compared to our country's data, it was observed that the prevalences of diabetes, thyroid diseases, asthma, cancer, and RA were higher with respect to the general population of the country.

Table 3: Comparison of age, sex, extrapulmonary organ involvement, and stage of disease in sarcoidosis patients grouped as presence of thyroid disease

	All patients (*n*=694)	Thyroid disease		*P*
		Absent (*n*=603)	Present (*n*=91)	
Age, mean±SD	42.9±11.8	42.2±12	47.6±11	0.001
Gender, *n* (%)				
Female	487 (70)	406 (83.4)	81 (16.6)	0.001
Male	207 (30)	197 (95.2)	10 (4.8)	
Extrapulmonary involvement, *n* (%)				
Absent	515	443 (86)	72 (14)	0.15
Present	179	160 (89.4)	19 (10.6)	
Sarcoidosis stages, *n* (%)				
0	15	13 (86.7)	2 (13.3)	0.53
1	406	354 (87)	52 (13)	
2	243	213 (88)	30 (12)	
3	26	20 (77)	6 (23)	
4	4	3 (75)	1 (25)	

SD: Standard deviation

Table 4: Comparison of age, sex, extrapulmonary organ involvement, and stage of disease in sarcoidosis patients grouped as presence of rheumatoid disease

	All patients (*n*=694)	Rheumatoid disease		*P*
		Absent (*n*=673)	Present (*n*=21)	
Age, mean±SD	42.9±11.8	43±12	47±4	0.021
Gender, *n* (%)				
Female	487 (70)	467 (95.9)	20 (4.1)	0.007
Male	207 (30)	206 (99.5)	1 (0.5)	
Extrapulmonary involvement, *n* (%)				
Absent	515	501 (97.3)	14 (2.7)	0.45
Present	179	172 (96.1)	7 (2.7)	
Sarcoidosis stages, *n* (%)				
0	15	14 (93.3)	1 (6.7)	0.31
1	406	394 (97)	12 (3)	
2	243	236 (97)	7 (3)	
3	26	26 (100)	0	
4	4	3 (75)	1 (25)	

SD: Standard deviation

While diabetes, asthma, and thyroid diseases were more frequent in female patients, at advanced ages, diabetes, asthma, thyroid diseases, RA, and malignancy were more frequent. Among malignancies, the most frequent were gynecological cancers and the second was lung cancer. It was noteworthy that the diagnosis of malignancy was often made after the diagnosis of sarcoidosis. No relationship was found between the stage of sarcoidosis or extrapulmonary organ involvement with comorbid diseases that were frequent with respect to the general population of the country.

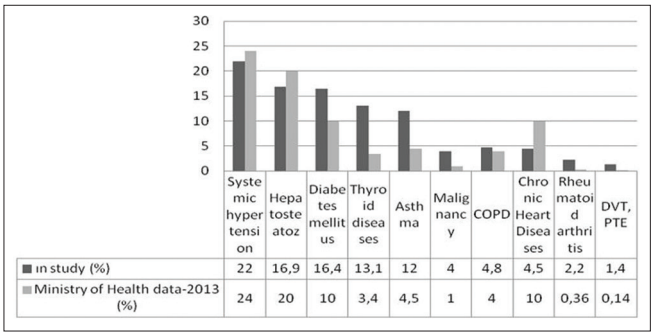

Figure 2: Comparison of Ministry of Health data with comorbid diseases in sarcoidosis patients

Studies report the frequency of comorbidity at a wide range of 29%–90% in sarcoidosis. Age, gender, race, and the stage of the disease have been identified as factors that influence the frequency of comorbidity.[15-18] In one study that investigated 1779 sarcoidosis patients, a comorbid disease was detected in 54% of the patients. In this series, it was identified that the most frequently detected comorbidities, namely hypertension, thyroid diseases, and diabetes mellitus occurred in patients of old age and those with multiorgan involvement.[16] Westney *et al*. detected comorbidities in the majority (90%) of African-American sarcoidosis patients. These have been determined as hypertension, diabetes, anemia, and asthma in that order of frequency. It has been stated that these diseases are seen particularly in women and patients with advanced-stage lung sarcoidosis. However, in this study, the fact that symptoms such as shortness of breath and coughing were coded based on the International Classification of Diseases (ICD)-9 coding system and included in the study as comorbidities could have caused the ratio to rise.[18] In our study, comorbidities were detected in the majority of the patients, and the most frequent diseases were hypertension, hepatosteatosis, diabetes mellitus, thyroid diseases, and asthma. The comorbid diseases detected frequently were more common in advanced age patients and female patients.

It is noted that the frequency of immune modulator-related diseases such as thyroid diseases and collagen vascular diseases is increased in sarcoidosis.[19,20] Epidemiological studies have shown that genetic tendency and environmental factors are triggers for the development of thyroid diseases as they are for sarcoidosis. In autoimmune thyroiditis, the production of IFN-γ and TNF-α cytokines originating from Th1-Ly increases. In many studies, it has been shown that thyroid functions are disrupted by mechanisms mediated by immune-mediators. This ratio has been reported as 3.7%–13.1%.[16,17,21] In the study conducted by Martusewicz-Boros *et al*., thyroid diseases are the second-most frequent comorbid disease.[16] Antonelli *et al*. have identified clinical hypothyroidism and Graves' disease at significantly higher rates in

sarcoidosis patients. In this study, being female and anti-thyroid peroxidase antibody positivity have been regarded as risk factors for thyroid diseases and these patient groups have been advised further thyroid tests.[19]

Table 5: Comparison of age, sex, extrapulmonary organ involvement, and stage of disease in sarcoidosis patients grouped as presence of malignant disease

	All patients (*n*=694)	Malignant disease		*P*
		Absent (*n*=666)	Present (*n*=28)	
Age, mean±SD	42.9±11.8	43±12	49±12	0.013
Gender, *n* (%)				
Female	487 (70)	467 (95.9)	20 (4.1)	0.53
Male	207 (30)	199 (96.1)	8 (3.9)	
Extrapulmonary involvement, *n* (%)				
Absent	515	491 (95.3)	24 (4.7)	0.22
Present	179	175 (97.2)	4 (2.8)	
Sarcoidosis stages, *n* (%)				
0	15	14 (93.3)	1 (6.7)	0.84
1	406	388 (95.6)	18 (4.4)	
2	243	235 (96.8)	8 (3.2)	
3	26	25 (96)	1 (4)	
4	4	4 (100)	0	

SD: Standard deviation

In their study in which they evaluated a number of comorbid diseases, they identified that only thyroid diseases were significantly more common with respect to the control group; they were two times more common than that in the general country population and three times more common than that in the control group.[17] In our series, thyroid diseases were the fourth-most common disease (13.1%); we had no control group, but they were found to be nearly 4 times more common with respect to the general population of the country (3.4%). Individuals with thyroid disease were older and most of them were female. The frequent concurrence of these two diseases appears to support the hypothesis of a common etiopathogenesis. We believe that it is necessary to perform more thorough assessments of thyroid diseases, particularly in women and elderly sarcoidosis patients. We may express that new prospective studies on this subject are needed.

In 15%–39% of sarcoidosis patients, muscle and joint involvement occurs.[1] Th1/Th17 cytokines play a major role in the pathogenesis of collagen tissue diseases such as RA, Sjögren's syndrome, and spondyloarthropathy.[7] Due to this similarity, sarcoidosis may mimic the clinical and laboratory findings of many collagen tissue diseases or may co-exist.[22] In an extensive case series conducted

Table 6: Between times of malignancy and detected sarcoidosis

	Prior sarcoidosis diagnosis (*n*=6)	After sarcoidosis diagnosis (*n*=18)	At diagnosis (*n*=4)	Total (*n*=28)
Gynecologic cancer	3	4	0	7
Lung cancer	0	4	2	6
Thyroid cancer	0	3	1	4
Pancreatic cancer	0	2	0	2
Brain cancer	0	1	1	2
Skin cancer	0	3	0	3
Breast cancer	2	1	0	3
Larynx cancer	1	0	0	1

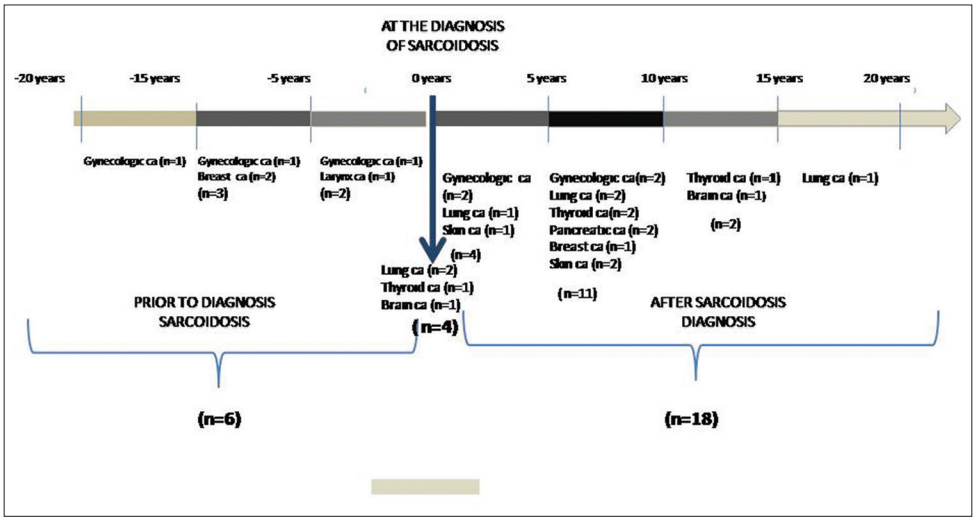

Figure 3: Malignant locations detected before, during, and after the diagnosis of sarcoidosis

based on the ICD-10 coding system, connective tissue diseases were detected in 6.2%–8.2% of cases.[15,16] In the study conducted by Boros *et al*., these diseases were seen more often in patients with multiorgan involvement. In our study, the diagnoses of comorbid diseases were not solely based on the ICD-10 coding system; we used clinically verified diagnoses. According to this, collagen tissue disease was detected in 21 (3%) patients, and RA accounted for most of the cases. According to the data of our country's Ministry of Health, this rate is above the country's average. Sarcoidosis itself may cause joint involvement. However, it must not be forgotten that joint complaints could be due to a comorbid rheumatological disease and, when suspected, clinical assessment should be performed in cooperation with the rheumatology clinic.

Although the etiology of sarcoidosis is not understood completely, it is thought that allergic mechanisms may play a role and increase bronchial hyperreactivity. Restrictive lung disease is the basis of sarcoidosis, and it is often accompanied by airway obstruction. While Th2-derived cytokines are dominant in the immunology of asthma and Th1 helper-derived cytokines are dominant in sarcoidosis, the stimulation of cytokines in sarcoidosis increases the release of immunoglobulin E-mediated allergic mediators from B-lymphocytes.[23] Young *et al*. have shown that the bronchial hyperreactivity caused by histamine is increased in patients with sarcoidosis.[24] Studies have reported the prevalence of asthma between 2.2% and 15% in sarcoidosis.[16-18] The ratio of these patients was 12% in our series, and asthma was among one of the five most common diseases. The incidence of concomitant asthma in patients with sarcoidosis was higher in our study population compared to our country average. Similar to our study, Westney *et al*. have identified asthma as the fifth-most common comorbid disease (15%). In this series, it was seen that among all comorbid diseases, only asthma was significantly common among women. In the same study, no relationship was established between asthma and the stage of sarcoidosis.[18] The fact that asthma is one of the frequent comorbidities has suggested that sarcoidosis and allergic mechanisms are associated. We believe that prospective studies that investigate both the frequency of asthma and the effect of asthma on the prognosis of sarcoidosis are needed.

The relationship between sarcoidosis and cancer has been debated for years, but no consensus has been reached.[9-11,25] The oldest epidemiological study that researched this topic was performed in 1974 by Brincker and Wilbek. In this study, it was reported that malignant lymphoma increased by 11 and lung cancer increased by 3 times.[26] In studies conducted with extensive case series, the frequency of malignancy has been reported as 1.9%–10%.[15-17,27] In the study conducted by Ji *et al*. including 10,037 patients, the relationship between the number of hospitalizations and the development of malignancy was researched, and they reported the frequency of malignancy as 10% at 12-year follow-up.[27] They demonstrated that the risk of cancer increased as the number of hospitalizations and age increased. They attributed this condition to the chronic nature and severity of the disease. On the other hand, in two separate studies conducted in Denmark, it was reported that the risk of malignity did not increase in extensive case series followed for long periods such as 25 and 30 years.[25,28] In our study, the frequency of malignancy in sarcoidosis patients was identified as 4%, and this ratio is similar to the literature. Although we did not perform a comparison to a control group, the general frequency of malignancy reported in our country (1%) was lower with respect to the sarcoidosis patients. The most accepted hypothesis about this subject is that malignancy is triggered by impaired immune system functions and chronic inflammation.[9,10] The fact that most of the malignancies in our study developed after the diagnosis of sarcoidosis brought forward the opinion that chronic inflammation may have a role in the development of malignancies. Only small case series about the development of malignancy concurrent with or before sarcoidosis are available. The most frequently reported malignancies before the diagnosis of sarcoidosis are testicular and breast cancers.[29,30] In our series, the cancers diagnosed before sarcoidosis was diagnosed were gynecological and breast cancers. Cancer in the most frequently involved organs in sarcoidosis was identified after and/or concurrent with the diagnosis of sarcoidosis. The results of studies conducted on the types of malignancy that develop in sarcoidosis patients vary. In an extensive case series, it has been expressed that the risk for lung, skin, stomach, colon, liver, and kidney cancers and lymphoma and leukemia is increased significantly.[9,10,27] In our study, the most frequently detected gynecological cancer was endometrial cancer which was followed by lung cancer in the second place. In sarcoidosis, among reproductive organs, the uterus is affected the most.[1] It has been identified that high ratios of interleukin IL-α and TNF-α are released in the female genital system as a response to chronic inflammation. It has been shown *in vivo* and *in vitro* that these cytokines transform normal epithelial cells into malignant forms.[31] These results have brought forward the thought that a careful assessment must be performed in female patients with sarcoidosis with respect to malignant diseases. Like other studies, in our study, the mean age of patients was higher with respect to patients without malignancy. However, when the age distribution of patients with malignancy is examined, it was seen that

16 patients were under the age of 50; in other words, the frequency of malignancy also increased among young sarcoidosis patients.

The limitations of the study are its retrospective nature and the lack of a control group. Its strong aspects are that it includes a high number of patients with a definite diagnosis of sarcoidosis that these patients are followed up by experienced chest specialists in the sarcoidosis polyclinic and that it is the first publication that investigates this topic in our country.

Conclusion

In final words, the rate of accompanying comorbidities is high in sarcoidosis. The frequency of diabetes, asthma, RA, thyroid diseases, and malignancy is higher with respect to the general data of our country. It must be kept in mind that thyroid diseases, RA, asthma, and malignancies may be seen more often particularly in sarcoidosis patients who are female or at an advanced age, and we believe that these patients should be evaluated with respect to these comorbid diseases. As all data were obtained retrospectively from the hospital database, no consent was obtained from the patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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