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60 years of sarcoidosis experience at an internal medicine clinic in Türkiye

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Ethics approval and consent to participate: this retrospective study was conducted in accordance with the Declaration of Helsinki. The research protocol and final form were reviewed and approved by the Ethics Committee of University of Health Sciences, Istanbul Haseki Research and Training Hospital (Approval #666328) on 14.07.2023. Due to the retrospective nature of the study and the use of fully anonymized, de-identified patient data, the requirement for informed consent to participate was waived by the institutional review board. Although the patient records included in this retrospective study were obtained from Cerrahpaşa Medical Faculty, the ethics committee application and approval were submitted through the University of Health Sciences, Istanbul Haseki Research and Training Hospital, where the lead investigator was affiliated at the time of the study. The ethics committee application explicitly identified Cerrahpaşa Medical Faculty as the source of the patient records and described the retrospective review of these records. Therefore, the difference between the institution providing the data and the institution whose ethics committee reviewed the study reflects the institutional affiliation and ethics review process, rather than a change in

the predefined data source or study population. The study was conducted in accordance with the protocol submitted to and approved by the ethics committee, and no data outside the scope described in the ethics application were used.

Informed consent: due to the retrospective nature of the study and the use of fully anonymized, de-identified patient data, the requirement for informed consent to participate was waived by the institutional review board and the ethics committee.

Patient consent for publication: this retrospective observational study was approved by the Ethics Committee of the University of Health Sciences, Istanbul Haseki Research and Training Hospital (Approval #666328). The requirement for informed patient consent for publication was waived due to the retrospective nature of the study and the use of anonymized/de-identified patient data.

Availability of data and materials: the data used in this study were obtained from Istanbul University-Cerrahpasa under specific permissions and are not publicly available. Requests for access should be directed to Istanbul University-Cerrahpasa.

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Abstract

Sarcoidosis is a multisystemic granulomatous disease with a variable clinical presentation and prognosis. This study aimed to evaluate the demographic characteristics, clinical features, diagnostic methods, and extrapulmonary manifestations of sarcoidosis in patients followed at a single center over a 60-year period to better understand the features of sarcoidosis and its regional characteristics in Türkiye, since it is a disease with varying presentations in different regions of the world.

Archive findings of 720 patients diagnosed with sarcoidosis at Cerrahpasa Medical Faculty between 1964 and 2023 were retrospectively analyzed. Demographic data, chest radiographic stage, extrapulmonary involvement, diagnostic methods, and results of tuberculin skin and Kveim test results were included in the study. Results of human leukocyte antigen (HLA) analysis and bone marrow biopsy findings of the patients on whom these tests were performed were also included. Statistical analyses were performed using chi-square and Mann–Whitney U tests.

Women accounted for 67.3% of patients, and 79.2% of all patients were between 20 and 50 years of age. Stage I (52.9%) and stage II (28.3%) disease predominated at diagnosis. Transbronchial biopsy was the most common diagnostic method (43.6%). Löfgren's syndrome was observed in 17% of patients. Skin (32.9%) and ocular (13.6%) involvement were the most frequent extrapulmonary manifestations. Bone marrow granulomas were detected in 10% of biopsied patients. Several HLA antigens showed significant associations with sarcoidosis. PPD positivity was 30.9%, whereas the Kveim test was positive in 76.7% of tested patients.

According to our findings, sarcoidosis in Türkiye predominantly affects women aged 20–50 years and is usually diagnosed at stage I. Skin and eye involvement were the most common extrapulmonary manifestations, emphasizing the importance of systemic evaluation. The findings also support a genetic contribution to disease and demonstrate the value of histopathological confirmation, especially by transbronchial biopsy, in establishing the diagnosis.

Key words: sarcoidosis, extrapulmonary sarcoidosis, Kveim test, Löfgren's syndrome, cutaneous sarcoidosis, bone marrow biopsy.

Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown cause and it might affect many organs [1,2]. The disease runs a benign clinical course in many patients; however, progressive disease and fibrosis might develop in some cases [3,4]. Although the disease is generally encountered in adults of 20-40 years of age, it might occur at any age [5]. Because sarcoidosis can mimic other diseases and manifest in a vast variety of forms, it's important to understand clinical features of the disease.

In this study, we retrospectively evaluated the demographic and general clinical features, methods of diagnosis, and notable extrapulmonary organ involvements in 720 patients diagnosed as sarcoidosis within a 60-year-period in a single center to better understand the features of sarcoidosis and its regional characteristics in Türkiye since it is a disease with varying presentations in different regions of the world. Despite being a single center study, our patients can be considered a study population representing the whole of Türkiye, as our center is a tertiary reference center for sarcoidosis, in which patients from many different regions of Türkiye with various ethnic backgrounds are followed and treated.

Materials and Methods

Seven hundred and twenty patients diagnosed as sarcoidosis at the Cerrahpaşa Medical Faculty, internal medicine clinic between 1964 and 2023 were included into the study. Since this study consisted of a very long observation period of 60 years, during which sarcoidosis diagnostic criteria, staging conventions, and available technologies evolved substantially, it was important to determine a common diagnostic criteria for all the patients included in the study. The criteria in 1999 ATS/ERS/WASOG joint statement for sarcoidosis was used as the diagnostic standard, which was already used as the criteria for our patients from 1999 onward. Since the statement was released in 1999, patients who were diagnosed before 1999 were reevaluted according to ATS/ERS/WASOG statement. Those who fit the diagnostic criteria were included in our study while those who don't were excluded.

Diagnosis of sarcoidosis was based on clinical, radiological and histopathological grounds. The following criteria were necessary for diagnosis: presence of noncaseating granulomas in the histological examination of at least one tissue specimen, the absence of mycobacteria and fungi in cultures, and the exclusion of other granulomatous diseases. The patients' age, sex, presence of extrapulmonary involvement, stage of disease according to chest X-ray, and the

results of Kveim and tuberculin skin tests when available were obtained from the medical records.

Chest X-rays were evaluated according to the classification of De Remee [6];

Stage I: Bilateral hilar lymphadenopathy (BHL)

Stage II: BHL plus parenchymal infiltration

Stage III: Parenchymal infiltration without hilar lymphadenopathy

Stage IV: Pulmonary fibrosis

50 (39 females, 11 males) of 92 consecutive patients diagnosed as sarcoidosis between 1997-2001 at our center had undergone bone marrow biopsy. We also evaluated whole blood counts and bone marrow biopsy results of these patients.

HLA class I and II antigens were studied in 64 of our sarcoidosis patients who came to our clinic between 1998-2001. The typing for HLA class I and II antigens were performed by complement-dependent lymphotoxicity test at the immunology laboratory of our center. One hundred-and-sixty donor candidates for kidney transplantation were taken as controls.

HLA and bone marrow biopsy procedures were performed as a routine test but only on a limited number of patients and within a specific timeframe because the authorization obtained for these tests- in accordance with national health regulations- was restricted to a specific duration and patient count.

Chi-square and Mann-Whitney U tests were used for statistical analysis.

Results

Of all patients, 484 (67.3%; 95% CI, 63.7–70.6%) were female and 236 (32.7%; 95% CI, 29.4–36.3%) were male. The demographic features of the patients are seen on Table 1. 79.2% (95% CI = 76.0–82.0%) of the patients were between 20-50 years of age.

At the time of initial diagnosis, more than half (52.9% ; 95% CI, 49.3–56.5%) of our 720 patients had stage I disease, and more than one fourth (28.3%; 95% CI, 25.2–31.7%) had stage II disease. The distribution of patients of both sexes into stages at the time of diagnosis is seen in Table 2.

In our study, the method most frequently method used for histopathological diagnosis of sarcoidosis was transbronchial biopsy (43.6%; 95% CI, 40.0–47.3%). Skin biopsy was another frequently used method (13.5%; 95% CI, 11.2–16.2%). Diagnostic methods used in our study are seen in Table 3.

In 122 (17.0%; 95% CI, 14.4–19.9%) of the patients the initial presentation of the disease was in the form of acute sarcoidosis (Löfgren's syndrome). 94 (77.0%; 95% CI, 68.8–83.6%) were female and 28 (23.0%; 95% CI, 16.4–31.2%) were male. Among patients with Löfgren's syndrome, erythema nodosum was present in 72.4% and arthritis or arthralgia in 51%. Periarticular ankle inflammation was observed in 62% of the patients with joint complaints. When 720 patients were considered, the most frequent extrapulmonary involvement in our sarcoidosis patients was that of the skin (32.9%; 95% CI 29.6–36.4%). The frequencies of involvement in other important extrapulmonary organs are seen in Table 4.

In patients whose hematologic data were evaluated, anemia was present in 11 (22.0%; 95% CI, 12.8–35.2%), while anemia accompanied by leukopenia was present in 3 (6.0%; 95% CI, 2.1–16.2%).

Bone marrow biopsy performed on 50 patients revealed noncaseating granulomas in 5 (3 males, 2 females, 10%) of the patients. Three of these patients had anemia and leukopenia-lymphopenia. The other 2 patients with bone marrow granulomas had normal blood counts. The frequency of HLA A2, A9, A24 (9), A25, B12, B22, B38, DR4, DR14 and DQ4 antigens was significantly higher in sarcoidosis patients when compared to the control group, and the frequency of HLA B7 and DR7 antigens was significantly lower. The comparison of HLA groups which were different in the sarcoidosis and the control group is seen in Table 5.

Tuberculin skin test (PPD) was performed in 551 subjects and Kveim test in 297 subjects. PPD test was positive in 170 (30.9%; 95% CI, 27.1–34.8%) patients. The frequency of PPD test positivity among females was 31.5% and among males it was 29.6%. Kveim test was interpreted as positive in 228 (76.7%; 95% CI, 71.6–81.2%) of the patients it was performed on. Kveim test was positive in 75.7% of females and 78.9% of males on whom it was performed on. The Kveim test was performed as a routine procedure during the period during the period when it was available. It could not be administered to all patients because the test material could no longer be obtained, and its use was discontinued due to concerns regarding potential health risks.

Discussion and Conclusions

720 patients who were diagnosed with sarcoidosis at our center within the last 60-year period were retrospectively evaluated. Approximately two thirds of our patients were females. The sex distribution shows a variability in different series. Although no prominent sex

predominance has been observed in some studies, it was reported that the frequency of females was higher in most series [3,7,8].

Sarcoidosis might be seen at any age, however, the peak incidence of the disease is generally between 20-40 years of age [3,4,9]. In one large series, 73% of male patients and 55% of female patients were between 20-40 years of age [10]. Another large series reported that 50% of the subjects were in this age group [9]. In our study, 62.8% of males and 53.2% of females were in the 20-40 age group (Table 1). 4% of our patients were over 60 years of age and 3.9% were younger than 20. In the large review mentioned above, 2% of the subjects were younger than 10 and 4% were older than 60 [10].

More than half (52.9%) of our patients with sarcoidosis had radiologic stage I disease at the time of initial diagnosis. The authors of a large study of more than 3000 patients stated that 51% of the cases had stage I disease radiologically at the time of diagnosis [11]. The same study also reported that 29% of the subjects had stage II disease. In our study, the ratio of patients with stage II disease was 28.3%-similar to the study above.

The most frequently used diagnostic method in our series was transbronchial biopsy (43.6%). Other methods we used frequently for diagnostic purposes were skin and lymph node biopsy. Both biopsy methods are less invasive and more easily applicable than other methods. Therefore, the presence of skin findings and lymphadenopathy should be carefully sought in cases suspected of having sarcoidosis and which need histologic confirmation. The frequency of positive results with transbronchial biopsy shows variability in different series. In one series, while the frequency of positive results with transbronchial biopsy in all stages of disease was 62%, it was 76% in stage II patients [12]. Another method used relatively frequent to reach the diagnosis in our study was mediastinoscopy. Although it is an invasive method, it is said that mediastinoscopy is diagnostic in 95-100% of the cases [13].

The clinical presentation of 17% of our sarcoidosis patients was in the form of Löfgren's syndrome. It is known that this type of presentation is more frequently observed in some geographical regions and in people of some ethnicities [14-16]. In one series from Denmark [1], 20% of the subjects and in another series from Germany [10], 8.4% of the subjects presented with Löfgren's syndrome. On the contrary, in one Spanish series nearly half of sarcoidosis patients presented with Löfgren's syndrome [14]. Arthritis and/or arthralgia was present in 51% of our patients with Löfgren's. The most common joint finding in our patients was periarticular ankle inflammation (62%). In one Löfgren series from Spain, 44% of the patients had periarticular ankle inflammation [17].

Cutaneous involvement of sarcoidosis was observed in almost one third (32.9%) of our patients. The most frequent (20.5%) skin lesion was erythema nodosum. Other skin lesions were skin plaques, subcutaneous nodules, maculopapular eruptions, scar lesions, lupus pemio and psoriasiform plaques. The frequency and the type of cutaneous involvement show variations among geographical regions and ethnicities [18,19]. In our study, patients with erythema nodosum, maculopapular rash and plaque lesions were found to be related less with lupus pernio compared to patients with other forms of skin lesions and patients with scar lesions were found to have more frequent parenchymal involvement than average. In accordance with the results of our study, we think that the evaluation of skin findings is important because this makes a contribution to diagnosis and also provides knowledge about the extent of the disease.

Different types of eye involvement might be encountered in sarcoidosis and it is said that eye involvement might be detected in 25% of the patients if a slit lamp is used [20]. The most frequent types of eye involvement are acute or chronic anterior uveitis (two thirds of patients with eye involvement), and less frequently (15%) posterior uveitis. Conjunctivitis, scleritis, lacrimal gland involvement, chorioretinitis, retinal hemorrhages are other types of eye involvement [21,22]. We detected eye involvement in 98 (13.6%) of our patients. The most frequent ocular finding was uveitis (62.2%).

Some autopsy and clinical series reported that noncaseating granulomas were detected in the bone marrow of 20-30% of sarcoidosis patients [23]. Although pancytopenia, thrombocytopenia, hemolytic anemia with or without splenomegaly have been reported in association with sarcoidosis, the most frequent hematologic abnormality is lymphopenia [24]. In our study, bone marrow involvement was found in 10% of the 50 patients who underwent biopsy. Three of these patients had anemia and lymphopenia, the other 2 patients had no hematologic abnormality. Therefore, it should be borne in mind that bone marrow involvement might be present without causing any hematologic abnormality and bone marrow biopsy makes a contribution to diagnosis in some cases. It should be noted that these findings should be accepted as descriptive findings, given the very limited sample size.

Some previous studies stated that there was a genetic predisposition to sarcoidosis and that the disease was associated with certain HLA antigens [25,26] In this study, the frequency of HLA A2, A9, A24 (9), A25, B12, B22 and B38 class I antigens and HLA DR4, DR14 and DQ4 class II antigens were found to be significantly higher in sarcoidosis patients than in the control group. The most frequent antigens in sarcoidosis patients were HLA B22, DR14, B12 and B38.

A very important finding is that HLA A9 antigen was detected in only sarcoidosis patients (12.5%), which implies that sarcoidosis is a genetically related disease. One previous study from our country had also reported an increased frequency of A9 antigen [27].

One of the important results of our study was that the positivity of Mantoux/PPD test was 30.9%, which was relatively high. One study from Ireland reported that Mantoux test positivity was 22% [28]. The higher frequency of Mantoux test positivity in our study might probably be explained by the higher incidence of tuberculosis in our country than in other countries. None of our patients with a positive Mantoux test had any sign of active tuberculosis. On the other hand, more than three fourths of the patients (76.7%) with an available Kveim test gave positive results for this test. However, it should also be noted that Kveim test was performed on a limited number of patients (297/720). The reason for that is while it was performed as a routine procedure during the period when it was available, it could not be administered to all patients because its use was discontinued later on due to concerns regarding potential health risks like transmission risk of some undefined agents or agents with long incubation periods, because of the difficulty to find standardized, validated reagents and because a high rate of positive results might be obtained by transbronchial biopsy [29].

This study has several limitations that should be considered when interpreting the findings.

First, its retrospective, single-center design, conducted at a tertiary referral center, may have introduced selection and referral bias and may limit the generalizability of the results to other patient populations and healthcare settings.

Second, not all investigations were performed in all patients, largely reflecting the retrospective nature of the study and the clinical indications at the time of evaluation; therefore, missing data may have influenced some of the observed associations. Especially, HLA and bone marrow biopsy procedures were performed only on a very limited number of patients and within a specific timeframe because the authorization obtained for these tests- which were performed as a routine during the time they were permitted- was restricted to a specific duration and patient count, and this limitation might raise concerns about selection bias. Kveim test was also performed on a limited number of patients, which might have caused selection bias.

Third, HLA typing was performed using an older methodology (complement-dependent lymphocytotoxicity), which may have provided lower-resolution or less comprehensive HLA characterization than currently available techniques (PCR/sequence-based methods). This is

a technical limitation affecting comparability with more recent HLA-association studies in sarcoidosis.

Finally, no formal adjustment for multiple statistical comparisons was performed for HLA comparisons, this is a limitation increasing the possibility of type I error and warranting cautious interpretation of statistically significant findings. These limitations should be taken into account when interpreting the results and should be addressed in future prospective, multicenter studies using standardized and contemporary diagnostic and HLA-typing methods with prespecified statistical analyses.

During a 60-year observation period, we saw that most of the sarcoidosis patients diagnosed were females of 20-50 years of age. Majority of our patients were diagnosed with stage I disease, and most frequent sites of extrapulmonary involvement were the skin and the eyes.

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Table 1. The distribution of our female and male sarcoidosis 720 patients according to age groups.

	Female	Male	Total	95% CI
n (%)	484 (67.3%)	236 (32.7%)		
Age (mean)	38.8	37.1	38.65	
Range	(10-70)	(10-66)	(10-70)	
Age groups				
<20, n (%)	21 (4.4%)	7 (3%)	28 (3.9%)	2.7-5.6
21-30, n (%)	110 (22.7%)	71 (30.1%)	181 (25.2%)	22.1-28.4
31-40, n (%)	148 (30.5%)	77 (32.7%)	225 (31.2%)	28.0-34.7
41-50, n (%)	110 (22.7%)	54 (22.8%)	164 (22.7%)	19.9-26.0
51-60, n (%)	73 (15%)	20 (8.5%)	93 (12.9%)	10.7-15.6
>60, n (%)	22 (4.4%)	7 (3%)	29 (4%)	2.8-5.7

Table 2. The distribution of sarcoidosis patients into disease stages at the time of initial diagnosis.

	Female	Male	Total	95% CI
Stage 0, n (%)	42 (8.7%)	14 (5.9%)	56 (7.7%)	6.0-10.0%
Stage I, n (%)	252 (52%)	129 (54.6%)	381 (52.9%)	49.3-56.5%
Stage II, n (%)	130 (26.8%)	74 (31.4%)	204 (28.3%)	25.2-31.7%
Stage III, n (%)	55 (11.4%)	16 (6.8%)	71 (9.9%)	7.9-12.3%
Stage IV, n (%)	5 (1)	3 (1.2%)	8 (1.1%)	0.6-2.2%

Table 3: The various methods employed to reach a histologic diagnosis of sarcoidosis

	Female	Male	Total	95% CI
Transbronchial biopsy, n (%)	204 (42.1%)	110 (46.6%)	314 (43.6%)	40.0-47.3%
Skin biopsy, n (%)	76 (15.7%)	21 (8.9%)	97 (13.5%)	11.2-16.2%
Lymph node biopsy, n (%)	55 (11.3%)	28 (11.9%)	83 (11.5%)	9.4-14.1%
Mediastinoscopic biopsy, n (%)	47 (9.7%)	31 (13.1%)	78 (10.8%)	8.8-13.3%
Liver biopsy, n (%)	24 (5%)	7 (3%)	31 (4.3%)	3.0-6.0%
Orbital mass biopsy, n (%)	14 (2.9%)	5 (2.1%)	19 (2.6)	1.7-4.1%
Parotid gland biopsy, n (%)	14 (2.9%)	7 (3%)	21 (2.9)	1.9-4.4%
Kveim test positivity, n (%)	39 (8%)	22 (9.3%)	61 (8.5)	6.7-10.7%
Clinical findings, n (%)	11 (2.3%)	5 (2.1%)	16 (2.2)	1.4-3.6%

Table 4. The major sites of extrapulmonary involvement.

	Female	Male	Total	95% CI
n	484	236	720	
Ocular involvement, n (%)	71 (14.7%)	27 (11.4%)	98 (13.6%)	11.3-16.3%
Uveitis, n (%)	45 (9.4%)	16 (6.9%)	61 (8.5%)	6.7-10.7%
Lacrimal gland inv., n (%)	10 (2.1%)	2 (0.8%)	12 (1.7%)	1.0-2.9%
Cutaneous involvement, n (%)	192 (39.7%)	45 (19.1%)	237 (32.9%)	29.6-36.4%
E. nodosum, n (%)	122 (25.2%)	26 (11%)	148 (20.5%)	17.8-23.7%
Lupus pernio, n (%)	17 (3.5%)	3 (1.3%)	20 (2.8%)	1.8-4.3%
M.papular rash, n (%)	19 (3.9%)	8 (3.3%)	27 (3.7%)	2.6-5.4%
Scar lesion, n (%)	16 (3.3%)	5 (2.1%)	21 (2.9%)	1.9-4.4%
Subcutaneous nodule, n (%)	26 (5.3%)	5 (2.1%)	31 (4.3%)	3.0-6.0%
Plaque lesion, n (%)	26 (5.3%)	4 (1.7%)	30 (4.1%)	2.9-5.9%
Parotid gland involvement, n (%)	28 (5.8%)	4 (1.7%)	32 (4.5%)	3.2-6.2%

Table 5. Distribution of HLA antigen types in sarcoidosis patients and in the control group

HLA type	Patients with sarcoidosis		Control		p
	n	%	n	%	
A2	36	56.3	54	33.8	0.002
A9	8	12.5	0	0	<0.001
A24[9]	18	28.1	15	9.4	<0.001
A25	9	14.1	5	3.1	0.004
A69[28]	3	4.7	0	0	0.02
B7	1	1.6	17	10.6	0.02
B12	21	32.8	5	3.1	<0.001
B22	13	20.3	2	1.3	<0.001
B38	5	7.8	1	0.6	0.008
B4921	3	4.7	0	0	0.02
DR4	23	35.9	33	20.6	0.017
DR7	2	3.1	27	16.9	0.006
DR14	11	17.2	2	1.3	<0.001
DQ2	10	15.6	7	4.4	0.009
DQ4	28	43.8	32	20.0	<0.001
DQ6	25	39.1	40	25.0	0.04