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Analysis of 275 patients with sarcoidosis over a 38 year period; a single-institution experience

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Summary
Background: Sarcoidosis is a systemic granulomatous disease with unknown etiology.
Objectives: We evaluated seasonal variation, demographic, clinical and diagnostic features of sarcoidosis in recently diagnosed symptomatic patients in the whole cohort (275 patients) and in the subgroups according to the estimated disease course (subacute course group vs. chronic course group). We also developed a prediction model to predict the course of sarcoidosis using simple clinical and demographic variables.
Material and methods: Two hundred and seventy-five patients with sarcoidosis.
Measurements and statistics: Roger's test, chi-square, t-test and *multiple logistic regression* were used.
Results: The distribution of cumulative monthly diagnosis was the lowest in November (fall) ($p<0.01$). Seasonal pattern was influenced by age and gender. Constitutional symptoms, stages 2 and 3 diseases and the absence of erythema nodosum were highly significant parameters for chronic course. Using these variables, the developed model had a specificity of 93.1% and its positive predictive value was 89.5%. Progression of the disease was documented 6.4% in subacute group vs. 32.1% in chronic group ($p=0.00001$). Preventive effect of smoking was more pronounced in females than in males in our cohort.
Conclusions: Further well-designed and large prospective studies are required to better understand the importance of these findings, and to validate the prediction model presented here.

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Introduction

Although genetic tendency, environmental factors and immunologic abnormalities are considered in the pathogenesis of sarcoidosis, the exact cause and the pathogenesis of disease remain unestablished.[1,2] In this study, we evaluated a large cohort of sarcoidosis patients with known date of onset of symptoms and estimated disease course over a 38 year period followed at a single medical center in Turkey (1966–2004).

Our aims were to show the seasonal variation, demographic, clinical and diagnostic features of sarcoidosis and, then, to develop a clinically useful prediction model to predict the course of sarcoidosis. We evaluated seasonal variation, demographic, clinical and diagnostic features of sarcoidosis in recently diagnosed symptomatic patients in the whole cohort (275 patients) and in the subgroups according to the estimated disease course (subacute course group vs. chronic course group). We also compared these subgroups with each other. Additionally, we developed a clinically useful prediction model to predict the course of sarcoidosis using simple clinical and demographic variables.

Patients and methods

Study population

We analyzed retrospectively medical records of the Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Lung Diseases, Istanbul between 1966 and June 2004. In our sarcoidosis clinic, we have used chart review system since 1964 which was adapted from the Mount Sinai School of Medicine Sarcoidosis Clinic.

The database contained full records of 492 patients with sarcoidosis which includes demographic features, presenting clinical features, initial diagnosis methods and the date and the age at the initial diagnosis for each patient. All patients were Turkish origin. Patients with the estimated disease course (subacute vs. chronic) were selected and included in this study (the cohort: 275 patients). These patients are still being followed prospectively according to the published criteria of WASOG (World Association of Sarcoidosis and Other Granulomatous Diseases)/ATS (American Thoracic Society)/ERS (European Respiratory Society) since 1999.[2]

Definitions and patient selection

Diagnosis of sarcoidosis

For each patient, sarcoidosis was diagnosed by a committee who were experts on sarcoidosis. This sarcoidosis committee included one senior sarcoidosis pulmonologist, three other pulmonologists and one pulmonary radiologist. Additionally, at the end of every year, the committee was gathered to re-evaluate all patients with sarcoidosis for progression and regression assessment.

The diagnosis of sarcoidosis was established when clinicoradiological findings were supported by histological evidence of non-caseating epithelioid cell granulomas in one or more than one organ system and exclusion of other disorders known to cause granulomatous disease. Mycobacteria and fungus were excluded by tissue stainings and cultures.

Selection of the patients

We evaluated the pattern of seasonality in the symptomatic, recently diagnosed patients with sarcoidosis. Patients with sarcoidosis diagnosed by chest X-ray scanning and not symptomatic were excluded. Some of the patients were diagnosed after Kveim–Siltzbach test.

Chest radiographs were classified as Scadding described: stage 0, normal chest radiographic findings; stage 1, bilateral hilar lymphadenopathy (BHL) alone; stage 2, BHL with pulmonary infiltrates; stage 3, pulmonary infiltrates only; stage 4, pulmonary fibrosis/fibrocystic parenchymal changes.[3] Löfgren's syndrome was defined as the association of erythema nodosum with BHL and/or right paratracheal lymphadenopathy with or without pulmonary infiltrates.[4]

We evaluated the pattern of seasonality only in the symptomatic, recently diagnosed patients with sarcoidosis. We have also recorded the dates of diagnosis for each patient. However, we did not use these dates in this study because the onset of symptomatic presentation of sarcoidosis is more useful than the dates of diagnosis for a seasonality study.

Distribution of the patients into the subgroups according to the course of the disease

The diagnostic methods employed in 275 patients were shown in Table 1. After the selection of patients, the cohort was divided into two groups by the estimated course of disease as follows: 115 patients in the subacute course group (if estimated duration time of disease was less than 2 years) and 160 patients in the chronic course group (if estimated duration time of disease was more than 2 years).[6] Of the 275 patients, seven patients were followed for 7–18 months, five patients had 18–24 months follow-up, and the rest of the cohort (263 patients) had more than 24 months follow-up.

The climate features of Turkey and the definition of seasons

This study was conducted in Istanbul, Turkey, a city with a continental climate and quite wide temperature differences between summer and winter.[5] Ninety-seven percent of Turkey lies in Asia and about 3% in Europe. The Asian part of the country is mainly a long peninsula, bound on the north by the Black Sea and on the south by the Mediterranean. Turkey has a relatively high altitude throughout the country. The Sea of Marmara divides the city into two parts: an Asian part and a European part. Istanbul is located in the western part of Turkey and has average temperatures of 42 F (6 °C) in January and 75 F (24 °C) in July.

The month of presentation was determined as the month symptoms first appeared. Seasons (quarters) defined in this study as follows: winter (January–February–March), spring

Table 1 Initial diagnostic procedures in 275 patients with sarcoidosis.

	Number with positive results/total number of biopsies (%)		
	Subjects with subacute course	Subjects with chronic course	Total
# Verified by histology from			
Transbronchial	47 (40.9%)	75 (46.9%)	122 (44.4%)
Mediastinoscopy	13 (11.3%)	23 (14.4%)	36 (13.1%)
Scalen lymph node	4 (3.5%)	5 (3.1%)	9 (3.3%)
Peripheral lymph node	9 (7.8%)	15 (9.4%)	24 (8.7%)
Skin	15 (13%)	16 (10%)	31 (11.3%)
Scar-skin	2 (1.7%)	1 (0.6%)	3 (1.1%)
Subcutan nodul	3 (2.6%)	2 (1.3%)	5 (1.8%)
Ocular	0	1 (0.6%)	1 (0.4%)
Parotis	1 (0.9%)	1 (0.6%)	2 (0.7%)
Muscle	0	1 (0.6%)	1 (0.4%)
Pleura	0	2 (1.3%)	2 (0.7%)
Liver	1 (0.9%)	2 (1.3%)	3 (1.1%)
Open lung	0	3 (1.9%)	3 (1.1%)
Nasal ethmoid	1 (0.9%)	2 (1.3%)	3 (1.1%)
Only Kveim	16 (13.9%)	11 (6.9%)	27 (9.8%)[a]
No histology			
BHL + erythema nodosum	3 (2.6%)	0	3 (1.1%)
Total number	115	160	275

[a]Statistically significant.

(April–May–June), summer (July–August–September) and fall (October–November–December).

Data analysis

The data were presented as mean $\pm$ SD. The monthly distribution of diagnosis was used to study seasonal variation by cumulative diagnosis per month during the full 38 year period. The graphical data presentation was based on the cumulative monthly averages during the 38 years, expressed as the percentage above or below the average monthly value during the entire study period. The amplitude of seasonal variation was described by the total seasonal variation. Total seasonal variations were measured as the sum of the percentage above the average for the month with the highest value and the percentage below the average for the month with the lowest value.

Statistical methods

Roger's test for cyclic variation was used to determine the significance of any seasonal variation of incidence.[7] This statistical analysis determines a simple harmonic cyclic trend, by dividing a circle into 12 equal sectors and plotting the monthly frequencies as co-ordinates (x and y) in the corresponding sectors in the circle. Additionally, *t-test* and *chi-square test* were used. A mathematical model was developed by *multivariate logistic regression test*. Probability (p) values <0.05 were considered as statistically significant.

Results

Demography of the cohort

Initial demographic features were shown in Table 2. Of the 275 patients, 190 (69%) were female, median age of the cohort was 40.2 ± 12.8 year. The majority of patients were in the third (29.4%) or fourth (24%) decade. The rest of the cohort was in the fifth (18.5%), second (16%), sixth (8%), and first (4%) decades, respectively.

Female patients were older than male patients (41.5 ± 13.4 year vs. 37.3 ± 11 year, respectively, $p = 0.008$). Erythema nodosum was more common in female patients than in males (33.1% vs. 20%, $p = 0.013$). Female patients were more common than males in the fifth decade age (22.1% vs. 10.5%, $p = 0.01$) while male patients were more common than females in the third decade age (22.6% vs. 44.7%, $p = 0.0001$).

Demography of the subgroups

Median age of the patients with subacute course was not different from that of the patients with chronic course. Median age of female patients in subacute course group was significantly different from that of the male patients while median age of female patients in chronic course group was not different from that of the male patients.

Clinical features in the cohort

Organ involvement was shown in Table 3. Demographic and clinical features consistent with sarcoidosis did not show any

Table 2 Demographic features in 275 patients with sarcoidosis.

	Subjects with chronic course	*p*-value (subacute vs. chronic)	Total (275 subjects)
Female/male (%)			
81/34	109/51	70% vs. 68%	190/85
(70.4%/29.6%)	(68.1%/31.9%)	$p > 0.05$	(69%/31%)
Mean ± SD for age			
♀: 40.2±12.9	♀: 42.4±13.7	39.9±11.9 vs.	♀: 41.5±13.4
♂: 38.9±9.4	♂: 36.3±11.9	40.3±13.5	♂: 37.3±11.0
$p = 0.005$[a]	$p > 0.05$	$p > 0.05$	$p = 0.008$[a]
Sarcoidosis in family			
3 (2.7%)	5 (3.2%)	$p > 0.05$	8 (3%)

[a]Statistically significant.

Table 3 Organ involvement.

	Subjects with subacute course	Subjects with chronic course	*p*-value (subacute vs. chronic)	Total (275 subjects)
Skin lesions	29 (26.1%)	41 (26.1%)	>0.05	70 (26.1%)
Respiratory symptoms	53 (47.7%)	100 (63.7%)	= 0.009[a]	153 (57.1%)
Superficial lymph node enlargement	19 (17.1%)	31 (19.7%)	>0.05	50 (18.7%)
Erythema nodosum	48 (41.7%)	32 (20%)	<0.001[a]	80 (29.1%)
Constitutional symptoms	34 (30.6%)	80 (51%)	= 0.001[a]	114 (42.5%)
Neurologic symptoms	3 (2.7%)	5 (3.2%)	>0.05	8 (3%)
Arthralgia/artritis	38 (34.2%)	34 (21.7%)	= 0.02[a]	72 (26.9%)
Ocular involvement	8 (7.2%)	21 (13.4%)	>0.05	29 (10.8%)
Hepatomegaly	11 (9.9%)	23 (14.6%)	>0.05	34 (12.7%)
Parotis/lacrimal gland involvement	Par.: 8 (7.2%)	Par.: 10 (6.4%)	>0.05	Par.: 18 (6.7%)
	Lac.: 2 (1.8%)	Lac.: 5 (3.2%)	>0.05	Lac.:7 (2.6%)
Poliüria	2 (0.9%)	1 (0.6%)	>0.05	3 (1.1%)
Splenomegaly	8 (7.2%)	13 (8.3%)	>0.05	21 (7.8%)
Myalgia	4 (3.6%)	9 (5.7%)	>0.05	13 (4.9%)
PPD anergy	78 (68%)	118 (74%)	>0.05	196 (72%)
Three or more than 3 organs involvement	6 (5.2%)	15 (9.4%)	>0.05	21 (7.6%)
Less than 3 organ involvement	109 (94.8%)	145 (90.6%)	>0.05	254 (92.4%)
Hand bone involvement[b]	3 (2.6%)	6 (5.2%)		9 (3.3%)
Hypercalcemia[b]	6 (5.2%)	8 (6.9%)		14 (5.1%)
Lupus pernio[b]	1 (0.6%)	6 (5.2%)		7 (2.6%)
Lactation/pregnancy[b]	6 (5.2%)	0		6 (2.2%)
Heart involvement[b]	2 (1.2%)	1 (0.6%)		3 (1.1%)
Macroscopic changes on the fingers[b]	3 (2.7%)	4 (2.5%)		7 (2.6%)
Löfgren's syndrome (without biopsy)[b]	3 (2.6%)	0		3 (1.1%)
Cancer development[b]	0	2 (1.2%)		2 (0.7%)

[a]Statistically significant.
[b]Statistical analysis was not applied for these parameters due to small sample size.

significant difference between patients with subacute vs. patients with chronic course except respiratory symptoms, erythema nodosum, constitutional symptoms, arthralgia and/or arhtritis, and stages 1, 2, and 3 diseases (Tables 2–4).

Patients were asked to recall the date of onset of symptoms of sarcoidosis. The diagnosis of sarcoidosis was made on the first physician visit in 49.1% of subjects. The diagnosis of sarcoidosis had been delayed for 2.077±3.851

month. Progression was noted in 21.8% of the patients while remission was noted in 60.4% of the patients within 19.6±21.1 month.

Of the 267 patients, 28.5% were smoker ($p<0.01$). There was a significant difference between female and male smokers (17.3% vs. 53.7%, $p<0.01$; respectively). There was no difference between smokers and non-smokers regarding progression or regression of the disease.

Table 4 Correlation between sarcoidosis patients with subacute course vs. chronic course.

	Subacute course	Chronic course
Stage 1[a]	65	47
Stage 2[a]	34	72
Stage 3[a]	5	27
Stage 4	0	2
Skin alone other than EN	6	5
Extrathorasic involvement other than skin lesions	8	4

[a]Statistically significant.

Male gender, stage 1 disease, constitutional symptoms, and scalene muscle involvement were more common in the group age at onset less than 40 years ($p<0.05$) while female gender, stage 2 disease, and skin involvement were common in the group age at onset greater than 40 years ($p<0.05$).

Seasonal variability in the cohort

Seasonal pattern of the cohort was shown in Table 5. The distribution of cumulative monthly presentations for the 275 patients showed a significant seasonal variation with Roger's test ($p<0.001$). Average monthly presentations differed by as much as 135.3%, ranging from a peak 78.9% above average in April (spring) to 56.3% below average in November (fall). The seasonal pattern of presentations was also influenced by some age groups and by both genders ($p<0.001$ for female and $p<0.01$ for male). The amplitude of the seasonal variation was meaningful among patients 30–39, 40–49, and 50–59 years of age ($p<0.001$, $p<0.05$, and $p<0.05$, respectively).

A spring peak at the presentations was observed in the patients by Roger's test ($p<0.001$). It differed by as much as 87.2%, ranging from a peak 57.1% above average in spring to 30.1% below average in fall. The distribution of presentations also showed a significant seasonal variation by the first

Table 5 Monthly percentage variations in 275 sarcoidosis subjects[a].

	All	Female	Male	Age categories					
				10–19	20–29	30–39	40–49	50–59	60–69
Total	275	190	85	11	44	81	66	51	22
Percentage	100	69.09	30.909	4	16	29.455	24	18.545	8
Jan.	−21.45	−36.84	12.941	−100	9.0909	−40.74	−45.45	17.647	9.091
Feb.	13.45	20	−1.176	9.0909	−18.18	62.963	9.0909	−29.41	9.091
Mar.	13.45	20	−1.176	336.36	−18.18	−70.37	−9.091	88.235	118.2
Apr.	78.91	76.84	83.529	9.0909	118.18	107.41	100	41.176	−45.45
May	52.73	38.95	83.529	9.0909	63.636	62.963	81.818	41.176	−45.45
Jun.	39.64	38.95	41.176	118.18	−18.18	48.148	81.818	64.706	−100
Jul.	−25.82	−24.21	−29.41	−100	−18.18	18.519	−100	−5.882	9.091
Aug.	−43.27	−43.16	−43.53	−100	−72.73	18.519	−81.82	−29.41	−100
Sept.	−17.09	−24.21	−1.176	9.0909	−45.45	−70.37	9.0909	−5.882	118.2
Oct.	−4	7.368	−29.41	9.0909	36.364	−25.93	9.0909	−29.41	9.091
Nov.	−56.36	−43.16	−85.88	−100	−18.18	−85.19	−27.27	−76.47	−45.45
Dec.	−30.18	−30.53	−29.41	−100	−18.18	−25.93	−27.27	−76.47	63.64
# Total season[b]	135.3	120	169.41	436.36	190.91	192.59	200	164.71	218.2
Roger's	0	0.0003	0.002107	0.1063	0.2633	0.000736	0.034715	0.015554	0.3849
	<0.001[c]	<0.001[c]	<0.01[c]	>0.05	>0.05	<0.001[c]	<0.05[c]	<0.05[c]	>0.05

[a]Data points represent cumulative data from 1966 through 2004. Seasonal variation was shown by all cases, by age and by genders. Percentage above or below the average monthly value.

[b]Sum of the percentage above the average for the month with the highest value and the percentage below the average for the month with the lowest value.

[c]Statistically significant.

and second half of the year (29.4% vs. −29.4%, $p<0.001$; respectively). The distribution of cumulative monthly presentations in the cohort showed a significant seasonal variation with Roger's test for all cases in patients with age at onset less than vs. greater than 40 years, $p<0.001$ and $p<0.01$, respectively.

Patients with subacute course vs. chronic course

The sites of initial diagnostic biopsies, symptoms and signs were shown in Tables 1, 2 and 3, respectively. The diagnosis of sarcoidosis was made on the first physician visit in 42.6% of subjects in subacute vs. in 53.75% of subjects in chronic ($p<0.05$). The diagnosis of sarcoidosis had been delayed for 2.091 ± 2.891 month in the subacute group vs. 2.067 ± 4.388 month in the chronic group ($p>0.05$).

Erythema nodosum, stage I disease and arthralgia and/or arthritis were more common in group with subacute course than in the group with chronic course ($p<0.05$ for all). On the contrary, stages II and III diseases, respiratory symptoms, constitutional symptoms and 20–29 years of age at the diagnosis were more commonly seen in group with chronic course than in the group with subacute course ($p<0.05$ for all). There were 16 patients (13.9%) in the subacute course group (vs. 6.8% in chronic course group, $p=0.026$) diagnosed by positive Kveim reaction. There was no difference regarding other features such as three-organ involvement, PPD anergy, Kveim reaction results or observed months. Of the patients, 28.3% in subacute and 28.6% in chronic course group were smoker ($p>0.05$).

Progression of the disease was noted 6.4% of patients in subacute group vs. 32.1% in chronic group ($p=0.00001$) while regression was noted 93.6% of the subacute patients vs. 38.2% in chronics ($p=0.00001$).

Predictors of severity at the presentation and a model to predict the course of sarcoidosis

Erythema nodosum, arthralgia and/or arthritis, and stage 1 disease were more observed in the subacute while respiratory and constitutional symptoms and stages 2 and 3 diseases were seen more frequently in the chronic group by chi-square test ($p<0.05$ for all). These independent variables by multiple logistic regression test showed only constitutional symptoms, stages II and III diseases, and the absence of erythema nodosum which were highly significant (Table 6). Using these variables, the model (constitutional symptoms, stage III disease, and the absence of erythema nodosum combination) has specificity of 93.1% and sensitivity of 68%. Positive and negative predictive value were 89.5% and 77.1%, respectively. Diagnostic probability of this model was 81.5%. Using constitutional symptoms, stage II disease, and the absence of erythema nodosum, the model has a specificity of 77.1% and a sensitivity of 67.6%. Positive and negative predictive value were 67.6% and 77.1%, respectively. Diagnostic probability of this model was 72%. The combination of erythema nodosum, absence of constitutional symptoms and stage I disease were selected as reference for these analysis. Positive predictive value of the last model was 22.9% for chronic course.

Seasonal variation in the group with subacute course vs. in the group with chronic course

Subacute subgroup: The distribution of cumulative monthly presentations in the subacute group showed a significant seasonal variation with Roger's test ($p<0.01$). Average monthly presentations differed by as much as 167%, ranging from a peak 98% above average in April (spring) to 69% below average in September (summer) (Fig. 1). A spring peak at the presentations was also observed by Roger's test ($p<0.01$). It differed by as much as 104%, ranging from a peak 67% above average in spring to 37% below average in summer. The distribution of presentations also showed a significant seasonal variation by the first and second half of the year (27% vs. −27%, $p<0.001$; respectively). The seasonal pattern of presentations was also influenced by some age groups and by female gender ($p<0.01$). The amplitude of the seasonal variation was statistically significant among patients 20–29 and 50–59 years of age ($p<0.05$ for both). The amplitude of the seasonal variation was also significant among patients with age at onset less than 40-year-old ($p<0.05$). Average monthly presentations differed by as much as 228%, ranging from a peak 169% above average in April to 59% below average in September.

Table 6 Multivariate logistic regression analysis for all demographic and clinical features.

	Sig.	OR	95% CI–OR	
			Lower	Upper
Stage 1 disease		1		
Stage 0 disease	0.132	2.158	0.793	5.877
Stage 2 disease	0.000[a]	2.887	1.603	5.200
Stage 3 disease	0.001[a]	5.562	1.938	15.963
EN[b] positive		1		
Absence of EN	0.036[a]	1.952	1.045	3.648
Absence of constitutional symptoms		1		
Constitutional symptoms positive	0.016[a]	1.971	1.137	3.417

[a]Statistically significant.
[b]Erythema nodosum.

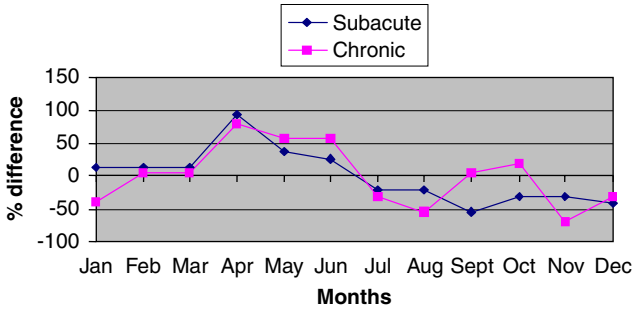

Figure 1 Monthly percentage variations in the subgroups (subacute vs. chronic). The reference value which is the average monthly value is 0%.

This significance was not observed among patients with age at onset greater than 40.

Chronic subgroup: Presentations for the patients in the chronic group showed a significant seasonal variation with Roger's test ($p<0.001$). Average monthly presentations differed by as much as 150%, ranging from a peak 80% above average in April (spring) to 70% below average in November (fall) (Fig. 1). A spring peak at the presentations was also observed by Roger's test ($p<0.001$). It differed by as much as 92.5%, ranging from a peak 65% above average in spring to 27.5% below average in both summer and in fall. The distribution of presentations also showed a significant seasonal variation by the first and second half of the year (27% vs. −27%, $p<0.001$; respectively). There was no difference between the subacute and chronic groups for the seasonal variations. The seasonal pattern of presentations was also influenced by one age group (30–39 years of age, $p<0.05$) and by both genders ($p<0.05$). The amplitude of the seasonal variation was significant among patients both less and more than age 40-year-old ($p<0.05$). Average monthly presentations differed by as much as 154%, ranging from a peak 100% above average in April to 54% below average in March, in August, and in November for patients with age at onset less than 40-year-old. Average monthly presentations differed by as much as 146%, ranging from a peak 60% above average in March, in April, and in June to 85% below average in November for patients with age at onset greater than 40-year-old.

Discussion

The World Congress in Kyoto, 1991 defined sarcoidosis as: a multisystem disorder of unknown cause. Both host and environmental factors may play important roles on the etiopathogenesis of disease.[8] Environmental factors are triggers of the onset of sarcoidosis in genetically susceptible individuals. In this regard, seasonal variation studies are important for infective agents and specific time periods.[9–15] In this study, we selected symptomatic newly diagnosed sarcoidosis patients for analysis regarding environmental risk factors. Additionally and not consistent with previous reports, we showed the months of the lowest level of presentation of sarcoidosis. Furthermore, we showed the influence of both gender and age on the seasonal variation of sarcoidosis.

Our results are consistent with an infectious and/or contagious etiology as previously reported for *Chlamydia pneumoniae*, *Propionibacterium acne*, *Mycobacteria*, wood burning, pine pollen, allergens, farm animals, fine sandy soil and clay eating.[9–15] However, our results further clarified this issue in favor of sarcoidosis. Observed seasonal variation with small peak in the winter differed markedly from the seasonal pattern of acute and chronic bronchitis, pneumonia, exacerbation of bronchiectasis and other common respiratory infections which shows winter predominance.[16–18]

Additionally, the seasonal pattern of mood changes as depressive episodes in fall and winter alternate with non-depressed periods in both spring and summer is on the opposite side of the seasonal pattern of sarcoidosis reported in our study although sarcoidosis is associated with an increased risk of depression.[19] Moreover, presenting symptoms within the subacute and chronic groups showed a similar seasonal pattern throughout the year. These findings lead us to consider similar triggering factors in the etiopathogenesis of sarcoidosis subgroups.[20]

It was reported that sarcoidosis usually presents in adults younger than 40 years old.[2] Our patients were, on the average, 10 years older than reported series. Genetic and/or environmental factors or the method of diagnosis might account for these differences between our patients and previous series.

A delay in the diagnosis of sarcoidosis might result in significant unnecessary health-care costs and may affect the outcome. The ACCESS Research Group have reported that the diagnosis of sarcoidosis is made on the first physician visit in only 15.3% of cases (vs. 49.1% in our study group).[21] This marked difference between the ACCESS group and our study mainly results from the patient selection criteria in these studies. The ACCESS group included all patients with sarcoidosis while we included only recently diagnosed patients with symptoms. We proposed that patients presenting with erythema nodosum, arthralgia and/or arthritis or respiratory complaints during the spring months of the year could benefit from a more thorough investigation to rule out sarcoidosis than a similar patient presenting in either summer or autumn or in that half of the year.

Association between sarcoidosis and smoking was questioned in this study. The prevalence of smoking in females and in males was 17.3% and 53.7%, respectively in this study while the prevalence of smoking was 38–49% in females and 51.5–65% in males in our population. Sarcoidosis appears to occur more commonly in female non-smokers than in male non-smokers. We proposed that preventive effect of smoking is more pronounced in females than in males at least in Turkey. These findings need further clarification.

Biochemical and genetic testing to predict the clinical course of sarcoidosis has been failed to predict the course so far. Furthermore, using the most sensitive, least invasive and expensive tests should be mandatory.[22,23] One of the purposes of this study was to find a simple and clinically useful model for predicting the course of sarcoidosis. In this regard, we showed that erythema nodosum, constitutional symptoms, and stages III and IV diseases can predict the course of the disease with a high degree of accuracy. Using these variables, we developed a mathematical model for the prediction of disease course by *multivariate logistic regression test*. Constitutional symptoms, absence of erythema

nodosum and stage II or III disease were the best predictor of chronicity. The least predictive combination for chronicity was the absence of constitutional symptoms, erythema nodosum and stage I disease.

Excellent prognosis features such as stage I disease, erythema nodosum and acute inflammatory manifestations were observed more frequently in our patients younger than 40 years. In contrast, stage II disease and skin involvement which are the features associated with chronic course were more common in the patients older than 40 years. Particularly, cancer cases were only seen among chronics.

Further well-designed and large prospective studies are required to better understand the importance of our findings and to validate the prediction model.

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