Seasonal Clustering of Sarcoidosis in Spring in Turkey

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Abstract

Some studies have observed a seasonal clustering of sarcoidosis cases in winter and early spring. In the preseent study, a relation was detected between the season of presentation and clinical, laboratory and radiological findings, in sarcoidosis.

Seventy nine patients were classified according to the season of presentation. Spirometry, laboratory, clinical, radiological findings and the required therapy were recorded.

The mean age was 45.2±15.5 years (15-78). Frequently seen seasons of presentation were spring (37%) and summer (29%), while rarely seen one was autumn (9%) (p:0.004). Frequently seen month of presentation was June (17.7%) (p:0.01). Three months; April, May and June, showed a peak of presentation (46%) in all year.

Frequently seen season of presentation in sarcoidosis was spring, where the least frequent one was autumn and frequently seen months of presentation were June, April and May in Izmir, Turkey. Symptoms, extrapulmonary involvement, symptom period, radiological stages, requirement of corticosteroide treatment, pulmonary function tests, serum ACE level, lymphocyte level in BAL, tuberculine skin test, serum and urine Ca level were not related to the season of sarcoidosis presentation. Sixty percent of the patients with sarcoidosis were tuberculine positive.

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Introduction

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body. Some studies have observed a seasonal clustering of sarcoidosis cases in winter and early spring (1). Seasonal clustering of sarcoidosis was reported in some surveys from both southern and northern hemisphere of the world. The peak of disease onset is March-May in London, March-April in Athen, January-June in northern Finland, April-June in Barcelona, April-August in Japan and August-December in New Zealand (2-6). We aimed to reveal that if there was a seasonal clustering of sarcoidosis in west part of Turkey. In the following, we detect a relation between the season and clinical, laboratory and radiological findings of patients.

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Materials and Methods

Patients

All patients diagnosed sarcoidosis between 1994 and 2003, were registered retrospectively. The diagnosis in all patients was based on the histological finding of noncaseating granulomata and/or the typical clinical appearance.

Patients' gender, age, pulmonary or extrapulmonary symptoms, stage of the disease (0 to 4), month of diagnosis, month of presentation, duration of symptoms, serum angiotensin converting enzyme (ACE) and calcium (Ca) levels, Ca level in 24 hour urine, tuberculine skin test, percentage of lymphocyte in bronchoalveolar lavage (BAL) fluid, first second forced expiratory volume (FEV_1), forced vital capacity (FVC) and the therapy were recorded. The seasonal clustering was analyzed without the evaluation of social and environmental factors.

Patients were classified according to the season of presentation. The season of presentation was determined as the month in which symptoms first appeared. December, January, February were grouped as winter, March, April, May as spring, June, July, August as summer and September, October, November as autumn.

Stages

Chest radiographs were performed in posterior anterior projection and were classified by one experienced reader in a standard manner according to the radiographic stage. Stage 0 was a normal chest radiography; Stage I had hiler adenopathy alone, Stage II had hiler adenopathy and parenchymal infiltrates; Stage III had parenchymal infiltrates alone; and Stage IV had evidence of focal fibrotic lesions with distortion of the lung parenchyma (1).

Statistics

The comparisons for the season and month of presentation were done using Chi-Square Goodness of Fit Test. Analysis according to the season of presentation comparing age, symptom period, ACE, FEV_1, FVC, FEV_1/FVC, lymphocyte in BAL, serum Ca and urine Ca were done using One-way ANOVA test. Pearson Chi-Square test was used in the analysis of pulmonary and extrapulmonary symptoms, stage, tuberculine test and corticosteroide treatment. Before the variance analysis, the normal distribution control of all variables using One-Sample Kolmogorov-Smirnov test and it was seen that no non-compliance had existed. If p value was under 0.05 and the minimum expected count was over 1, this result was considered to be significant statistically.

Results

Available data was provided from 72 (83.7%) female and 14 (16.3%) male, of 86 patients with sarcoidosis. Seven of them, who had no symptoms and/or whose season of disease presentation had not been learnt exactly, were excluded. The mean age was 45.2±15.5 years (15-78) in 79 patients.

Sarcoidosis was diagnosed using peripheral lymph node biopsy in 57 (66%), transbronchial lung biopsy and/or bronchial mucosa biopsy in 17 (20%), Ga67 scan in five (6%), skin biopsy in three (4%), mediastinoscopy in two (2%), video assisted thoracoscopic surgery in two (2%), parotid biopsy in one (1%), thoracotomy in one (1%), mediastinotomy in one (1%), while eight (9%) patients were diagnosed only with clinical and radiological findings.

Frequently seen seasons of presentation (in which symptoms first appeared) were spring (37%) and summer (29%), while rarely seen one was autumn (9%) (p:0.004). According to the month of presentation; frequently seen one was June (17.7%) (p:0.01) (Table 1 and Figure 1). Sixty five point eight percent of the patients showed a month of presentation in the first half of the year. Three months, April, May and June showed a peak of presentation with a percentage of 46% in all year.

Table 1. Month and the season of presentation in patients with sarcoidosis

Seasons and Months	Sarcoidosis n (%)	Total n (%)
Spring		
March	7 (8.9%)	29 (37%)
April	12 (15.2%)	
May	10 (12.7%)	
Summer		
June	14 (17.7%)	23 (29%)
July	5 (6.3%)	
August	4 (5.1%)	
Autumn		
September	2 (2.5%)	7 (9%)
October	3 (3.8%)	
November	2 (2.5%)	
Winter		
December	8 (10.1%)	20 (25%)
January	6 (7.6%)	
February	6 (7.6%)	
Total	79	p=0.004

The month of diagnosis were; January in seven (8%), February in three (4%), March in six (7%), April in six (7%), May in 10 (12%), June in nine (11%), July in 12 (14%), August in 12 (14%), September in seven (8%), October in seven (8%), November in two (2%) and December in five (6%) (Figure 2).

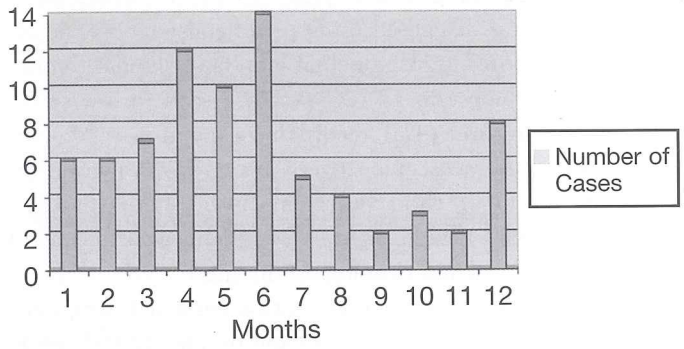

Figure 1. *The presentation month of the patients with sarcoidosis (p=0.01) (n=79).*

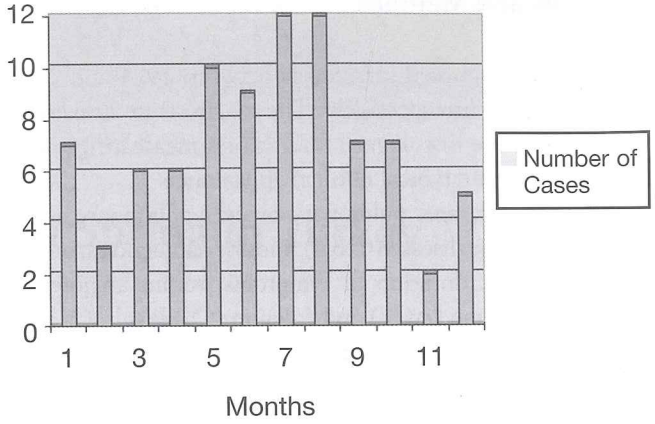

Figure 2. *The month of diagnosis in patients with sarcoidosis (n=79).*

Table 2. Patients' ages, symptom period, spirometry, serum ACE, BAL lymphocyte, urine and serum Ca levels according to the season of presentation

Parameter	Spring - n	Summer -n	Autumn - n	Winter - n	Total - n	p
Age (years)	43.2±15.6 (29)	42.1±14.4 (23)	54.8±12.9 (7)	48.3±16.5 (20)	45.2±15.5(79)	0.185
Symptom period (months)	2.73±2 (29)	4.08±3.9 (23)	6.57±5.2 (7)	4.06±3.8 (20)	3.8±3.5(79)	0.069
FEV_1 (%)	82.4±24.8 (17)	78.9±20 (14)	64±28.7 (6)	74.8±18.9 (14)	77.2±22.7(51)	0.378
FVC (%)	84.1±22.8 (17)	79.4±17.3 (14)	63.8±24.5 (6)	78.7±15.6 (14)	79±20.1(51)	0.211
FEV_1/FVC (%)	85.5±9.6 (17)	88±19.7 (14)	86.3±14.1 (6)	85.7±16.2 (14)	86.4±14.8(51)	0.971
ACE (mg/dl)	79.5±78.4 (17)	93.3±86.2 (8)	59.6±78.8 (3)	54±34.9 (10)	74.1±70.1(38)	0.665
BAL lymphocyte (%)	38±19.3 (20)	30±10.4 (14)	23.8±12.4 (5)	27±13.2 (11)	31.9±15.8(50)	0.132
Ca (mg/lt)	9.5±1.3 (13)	11.2±4.7 (10)	9.8±1.7 (4)	10.7±3.4 (10)	10.3±3.1(37)	0.605
Urine 24 hours Ca (mg/lt)	180.3±96.5 (12)	180±147 (8)	77.1±63 (4)	184.5±90.3 (7)	167.9±108.4(31)	0.372

(The data presents "Mean value ± Standard deviation")

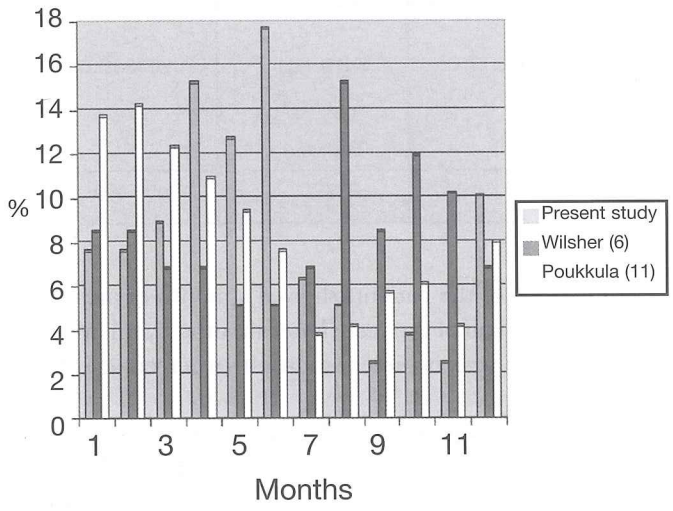

Figure 3. *The month of presentations in present and other studies. Wilsher (n=59, New Zealand), Poukkula (n=212, Finland), Present Study (n=79, Turkey)*

In patients, classified according to the season of presentation, there were no significant differences for symptom period, FEV_1, FVC, FEV_1/FVC, serum ACE level, percentage of lymphocyte in BAL, serum and urine Ca (Table 2).

There was no relation between the radiological stages and the season of presentation (p:0.918). Forty five (59.2%) of the patients required corticosteroide treatment and 31 (40.8%) did not. Three patients left before the decision of treatment. We did not find any significant difference for requirement of corticosteroide treatment between four seasons (p:0.385) (Table 3).

Frequently seen pulmonary symptoms were cough (62%), breathlessness (46%), chest and back pain (28%) and extrapulmonary symptom was weakness (37%). Pulmonary and extrapulmonary symptoms of the patients did not differ between four seasons (Table 4). Also there was not significant difference in occurrence of extrapulmonary involvement between four seasons of presentation. The incidence of extrapulmonary involvement in spring, summer, autumn and

Table 3. Radiological stages and requirement of corticosteroide treatment according to the season of presentation

Radiological Stage	Spring n (%)	Summer n (%)	Autumn n (%)	Winter n (%)	p	Total n (%)
0	0	1 (4.3%)	0	0		1 (1.3%)
1	10 (34.5%)	7 (30.4%)	2 (28.6%)	5 (25%)	0.918	24 (30.4%)
2	16 (55.2%)	13 (56.5%)	4 (57.1%)	12 (60%)		45 (57%)
3	3 (10.3%)	2 (8.7%)	1 (14.3%)	2 (10%)		8 (10.1%)
4	0	0	0	1 (5%)		1 (1.3%)
Required Corticosteroide Treatment	17 (58.6%)	15 (65.2%)	5 (71.4%)	8 (40%)	0.385	45 (59.2%)

Table 4. Pulmonary and extrapulmonary symptoms according to the season of presentation

Pulmonary Symptom	Spring n (%)	Summer n (%)	Autumn n (%)	Winter n (%)	p	Total n (%)
Cough	17 (58.6%)	13 (56.5%)	4 (57.1%)	15 (75%)	0.585	49 (62%)
Breathlessness	11 (37.9%)	11 (47.8%)	5 (71.4%)	9 (45%)	0.454	36 (46%)
Sputum	3 (10.3%)	4 (17.4%)	2 (28.6%)	5 (25%)	0.498	14 (18%)
Hemoptysis	2 (6.9%)	2 (8.7%)	1 (14.3%)	0		5 (6%)
Chest and back pain	8 (27.6%)	6 (26.1%)	2 (28.6%)	6 (30%)	0.994	22 (28%)
Extrapulmonary Symptom						
Weight Loss	1 (3.4%)	2 (8.7%)	0	3 (15%)		6 (7.6%)
Sweating	2 (6.9%)	0	0	2 (10%)		4 (5.1%)
Fever	3 (10.3%)	1 (4.3%)	0	2 (10%)		6 (7.6%)
Weakness	12 (41.4%)	8 (34.8%)	2 (28.6%)	7 (35%)	0.911	29 (37%)
Abdominal pain	1 (3.4%)	2 (8.7%)	0	2 (10%)		5 (6.3%)
Headache	1 (3.4%)	2 (8.7%)	0	1 (5%)		4 (5.1%)
Erythema nodosum	6 (20.7%)	3 (13%)	0	0		9 (11%)
Arthralgia	7 (%24.1)	5 (%21.7)	0	0		12 (%15)
Lack of appetite	6 (20.7%)	2 (8.7%)	1 (14.3%)	1 (5%)	0.377	10 (13%)
Nausea and vomiting	1 (3.4%)	0	0	0		1 (1.3%)
Pruritus	0	1 (4.3%)	0	0		1 (1.3%)
Facial nerve paralysis	1 (3.4%)	0	1 (14.3%)	0		2 (2.5%)
Eye complaints	2 (6.9%)	1 (4.3)	0	0		3 (3.8%)
Palpitation	0	1 (4.3%)	1 (14.3%)	0		2 (2.5%)
Dysphony	0	0	1 (14.3%)	0		1 (1.3%)
Total	29	23	7	20		79

winter was %82.8 (24), %87 (20), %100 (7) and %70 (14) respectively (p:0.27), while the total incidence was %82.3 (65) (Table 5).

Of the patients with sarcoidosis, 60% were tuberculine positive and 40% were negative. According to the season of presentation, tuberculine skin test results did not differ significantly (p:0.515) (Table 6).

Discussion

The results of this study reveal that; the frequently seen season of presentation in sarcoidosis is spring (37%), where the least frequent one is autumn (9%) and frequently seen months of presentation are June (17.7%), April (15.2%) and May (12.7%). Symptoms, extrapulmonary involvement, symptom period, radiological stages, requirement of corticosteroide tre-

Table 5. Extrapulmonary involvement in seasons of presentation

Extrapulmonary Involvement	Spring n (%)	Summer n (%)	Autumn n (%)	Winter n (%)	Total n (%)	p
Peripheral lymph node	21 (72.4%)	15 (65.2%)	6 (85.7%)	12 (60%)	54 (68.4%)	0.58
Eye	4 (13.8%)	2 (8.7%)	0	0	6 (7.6%)	
Skin	1 (3.4%)	1 (4.3%)	2 (28.6%)	0	4 (5.1%)	
Parotid gland	3 (10.3%)	2 (8.7%)	0	1 (5%)	6 (7.6%)	
Nervous system	2 (6.9%)	0	2 (28.6%)	0	4 (5.1%)	
Bone	1 (3.4%)	0	0	2 (10%)	3 (3.8%)	
Kidney	0	1 (4.3%)	0	0	1 (1.3%)	
Liver	2 (6.9%)	1 (4.3%)	1 (14.3%)	1 (5%)	5 (6.3%)	0.8
Spleen	0	1 (4.3%)	0	1 (5%)	2 (2.5%)	
Pleura	0	1 (4.3%)	0	01 (1.3%)		
Erythema nodosum	6 (20.7%)	5 (21.7%)	0	1 (5%)	12 (15.2%)	
Total of patients (n)	29	23	7	20	79	

Table 6. Tuberculine skin test results according to the season of presentation

Tuberculine Skin Test	Spring n (%)	Summer n (%)	Autumn n (%)	Winter n (%)	Total n (%) p=0.515
Positive (1-9mm)	14 (60.9%)	7 (58.3%)	5 (83.3%)	4 (44.4%)	30 (60%)
Negative (≥10mm)	9 (39.1%)	5 (41.7%)	1 (16.7%)	5 (55.6%)	20 (40%)

atment, FEV_1, FVC, FEV_1/FVC, serum ACE level, percentage of lymphocyte in BAL, tuberculine skin test, serum and urine Ca level are not related to the season of presentation.

Sarcoidosis occurs throughout the world, affecting all genders, races and ages. The epidemiology of sarcoidosis remains problematic for several reasons (1). Some studies have observed a seasonal clustering of sarcoidosis cases in winter and early spring (7,8). The peak of presentation are on March-May in London, on March-April in Athen, on April-June in Barcelona, on April-August in Japan (9).

In a population-based study, it was reported that seasonal variation in sarcoidosis incidence had been minimal, with a seasonal peak of 31% of the Rochester cases being diagnosed during the spring (March-May) (10). We detected a peak of presentation on April-June with a percentage of 46%, nearly equivalent to the half of all cases, diagnosed in one year, in Turkish patients.

Poukkula, et al (11); reported that sarcoidosis had begun and had been diagnosed more often in the first half of the year (64.2%) than in the second half (35.8%). Similarly in this study, symptoms of sarcoidosis onset had begun more often in the first half (65.8%) than in the second (Figure 3). Poukkula et al (11); also resulted that the cases with erythema nodosum (EN) had been commoner in January-June. Fite et al (4); pointed the high incidence of Lofgren's syndrome in springtime, in Catalonia. We diagnosed 12 patients of sarcoidosis presenting EN and 11 (91.6%) of them had the presentation of disease between March and August.

Wilsher (6); reporting a seasonal clustering in the southern hemisphere suggesting a common environmental trigger in the etiology of sarcoidosis, marked that the patients with EN or arthralgia alone had presented exclusively between April and December, with peak clustering in the spring months of August, September and October ($p<0.001$). Wilsher found no evidence of seasonal clustering in patients presenting with other than EN or arthralgia. In another study from Ankara, Turkey, Karakaya et al (12); evaluated 50 patients with sarcoidosis to search whether there was a seasonal clustering of onset or not. They reported that determination of the onset or the diagnosis time in sarcoidosis, presenting both with EN and/or arthalgia and with other symptoms, was significantly more common in spring and summer. Present study also marked these two seasons, spring (37%) and summer (29%) as the most common seasons of presentation while rarely seen one was autumn (9%). This tendency of presentation in two seasons was statistically significant ($p=0.002$). According to the month of presentation; frequently seen one was June (17.7%) ($p=0.01$). On the other hand, there was not significant difference in occurrence of extrapulmonary involvement, including EN, between four seasons of presentation.

Panayeas, et al (13) from Greece; reported a peak incidence in the early spring months; March and May. This assessment from Greece, a border neighbor of Turkey, was nearly the same with this study's results; three months, April, May and June, toget-

her showed a peak of presentation with a percentage of 46%. Sarcoid arthritis was found clustered in March-July (14,8). The seasonal clustering and the association with specific HLA class II antigens support the hypothesis that it results from exposure of susceptible hosts to environmental agents through the lungs (14).

In sarcoidosis, 1,25-DHCC is abnormally regulated throughout the year, with a significantly higher serum level in the summer season. Uncontrolled production of 1,25-DHCC in sarcoid pulmonary alveolary macrophages is possibly responsible for hypercalcaemic episodes, and this parameter should be used as a marker of disease activity (15). There were no significant differences for levels of serum Ca and urine 24 hours Ca, between four seasons, in sarcoidosis patients. Also symptom period, FEV_1, FVC, FEV_1/FVC, serum ACE level, percentage of lymphocyte in BAL did not differ in these seasons.

Besides no difference of tuberculine skin test results between four seasons, 60% of the patients with sarcoidosis were tuberculine positive. We think that the reason may be the high incidence of tuberculosis infection in population, in Turkey.

In conclusion; frequently seen season of presentation in sarcoidosis is spring, where less frequent one is autumn and frequently seen months of presentation are June, April and May, in Izmir, in Turkey. Pulmonary and extrapulmonary symptoms, extrapulmonary involvement, symptom period, radiological stages, the requirement of corticosteroide treatment, pulmonary function tests, serum ACE level, lymphocyte level in BAL, tuberculine skin test, serum and urine Ca level are not related to the season of sarcoidosis presentation. A further study evaluating age, gender, race, familial association, geographical variation, migration, climate, season and socioeconomic status together, will help to make more detailed definition of the disease in one country population.

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Abbreviations:

- serum angiotensin converting enzyme (ACE)
- calcium (Ca)
- bronchoalveolar lavage (BAL)
- first second forced expiratory volume (FEV_1)
- forced vital capacity (FVC)
- erythema nodosum (EN)