ORIGINAL ARTICLE

Late-onset and Rare Far-advanced Pulmonary Involvement in Patients with Sarcoidosis in Taiwan

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Background: Sarcoidosis is still considered a rare multisystem disorder in Taiwan, and data on the disease course and outcome are limited. We analyzed the clinical manifestations, disease course and complications in Taiwanese patients with sarcoidosis.

Methods: A retrospective cohort design was used. Fifty-six patients with sarcoidosis diagnosed between 1985 and 2004 were included. Their clinical features, laboratory findings at initial presentation, disease course, and complications were analyzed.

Results: Forty-three patients (76.8%) were female. The mean age at symptom onset was 47 years. The most common clinical symptoms were pulmonary (82.1%), cutaneous (23.2%), ophthalmic (19.6%), and articular (17.8%). Only two patients presented with Löfgren's syndrome. There was a seasonal variation in disease onset, with higher incidence in winter and early spring. No advanced pulmonary involvement was noted. Elevated levels of serum angiotensin converting enzyme (sACE) were found in 72.5% (29/40) of patients with active sarcoidosis, and significantly higher levels of sACE were found in patients with lung involvement (27.98 ± 1.71 IU/L vs. 18.2 ± 2.76 IU/L; $p < 0.01$). In 50% (20/40) of patients, sACE levels declined significantly in parallel with clinical remission (24.75 ± 1.53 IU/L vs. 16.33 ± 1.21 IU/L; $p < 0.05$). Spontaneous complete remission was found in 20.7% of patients, whereas 39.6% of patients with multiple extrapulmonary involvement responded poorly to intensive corticosteroids plus various immunosuppressants.

Conclusion: In this series, the mean age of disease onset was in middle age (mean, 47 years old), there was a low incidence of Löfgren's syndrome (3.6%), and no patients had advanced pulmonary syndrome. The results of this study also suggest that sACE might be a marker of pulmonary involvement that is also useful in monitoring disease activity. [*J Formos Med Assoc* 2006;105(4):269–276]

Key Words: clinical manifestations, disease course, prognosis, sarcoidosis

Sarcoidosis is a systemic disorder of unknown cause characterized by its pathologic hallmark, the non-caseating granuloma.[1] This disease can be self-limiting or chronic, with episodic recrudescence and remission.[1] Most patients report either acute or insidious respiratory problems, variably accompanied by symptoms affecting the skin, eyes, or other organs. Sarcoidosis occurs worldwide, affecting persons of all races and ages, and both genders. It has a particular proclivity for adults under the age of 40 and for certain ethnic and racial groups.[1] The reported prevalence of sarcoidosis ranges from less than 1 case to 40 cases per 100,000 population, with an age-adjusted annual incidence in the United States of 10.9 per 100,000 for whites and 35.5 per 100,000 for blacks.[1,2] In Taiwan, sarcoidosis is still considered a rare disease, although Perng et al reported increasing incidence in recent

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years, from 0.25 per 100,000 admissions to 2.7 per 100,000 admissions.[3] Data about the disease course and outcome of sarcoidosis in Taiwan are limited. Ever since Liberman first reported elevations of serum angiotensin converting enzyme (sACE) activity in sarcoidosis patients,[4] efforts have been made to determine its role in this inflammatory disease. The levels of sACE may collate with radiologic and clinical abnormalities,[4] but few studies have examined its relationship with clinical manifestations.

This study analyzed the clinical manifestations and laboratory findings at initial presentation, the disease course, and prognosis of 56 patients with sarcoidosis, and investigated the relationship between sACE and clinical manifestations and prognosis.

Methods

Patients

Fifty-six patients with sarcoidosis diagnosed at Taichung Veterans General Hospital between January 1985 and January 2004 were included. The diagnosis was established in accordance with the following criteria:[5] (1) histologic evidence of noncaseating granulomas in affected tissues; (2) clinical signs or symptoms consistent with sarcoidosis, that is, bilateral hilar lymphadenopathy and erythema nodosum and/or arthritis. Individuals with fungal disease, active tuberculosis, or who were taking antituberculosis therapy were excluded. This study was approved by the institutional review board of Taichung Veterans General Hospital.

Table 1. Criteria of sarcoidosis activity*

- Clinical features consistent with sarcoidosis†
- Abnormalities on chest radiograph (mediastinal lymphadenopathy or pulmonary infiltration)
- Increased serum angiotensin converting enzyme level
- Increased gallium-67 scan uptake (or liver uptake)

**Presence of, or changes in, any of the listed criteria constitutes evidence of disease activity; †skin lesions (erythema nodosum or granulomas), polyarthralgia/arthritis, respiratory symptoms (cough, dyspnea), fever, uveitis, hepatosplenomegaly, parotid enlargement, upper respiratory tract involvement, neurologic symptoms.*

Clinical method

A retrospective cohort design was used. Information about the clinical manifestations and disease course of all patients were collected, using standardized definitions and a standardized data extraction form. Chest radiography was performed at the time of initial diagnosis. Staging used the modified Scadding system[6] as follows: stage 0, normal; stage I, bilateral hilar lymphadenopathy; stage II, hilar lymphadenopathy with pulmonary infiltration; stage III, pulmonary infiltration only; and stage IV, end-stage pulmonary fibrosis.

Measurement of sACE level and gallium-67 scan were conducted in only 40 patients at initial diagnosis. Gallium-67 scan was also performed in those patients with hilar enlargement on chest radiograph. ACE was measured by the colorimetric method (ACE color; Fujirebio Diagnostics Inc, Tokyo, Japan). The clinical disease activity of sarcoidosis was defined as described previously (Table 1).[6] The decision to treat was based on the following criteria: (1) progressive change on chest radiographs or diffuse pulmonary involvement; (2) impairment of organs other than the lungs; and (3) persistent symptoms combined with parameters indicative of disease activity. Medication was given with corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate, and/or other immunosuppressive agents as necessary.

Follow-up study

The average follow-up duration was 7.2 years (range, 1–20 years). Fifty-three of 56 patients with sarcoidosis underwent repeat chest radiography at least every 6 months during the follow-up period after diagnosis. Complete remission was defined as normalization of chest radiograph and resolution of clinical manifestations, including the cutaneous, ocular and articular involvement. Partial remission was defined as unchanged or improved chest radiograph findings, defined as stage ≥ 1, and/or stabilized clinical manifestations. Persistent course was defined as deterioration of chest radiograph findings, defined as ≥ 1 stage worsen-

ing at the end of the follow-up period, or persistent or progressive clinical symptoms without response to treatment. Relapse was defined as deterioration of chest radiograph findings after stabilization for 6 months or worsening of clinical symptoms after resolution or stabilization for 6 months. In patients with complete or partial remission, the average period of sACE measurement was 6 months after the patient was symptom-free or in a stable condition. In patients with relapse, the average period of sACE measurement was 1 month after symptoms progressed.

Statistical analysis

Results were expressed as mean ± SEM unless otherwise specified. Differences among groups were determined by the Kruskal-Wallis test for nonparametric analysis of variance. Correlations among different variables were determined with multiple logistic regression. The Wilcoxon signed-rank test was used for comparison of sACE levels during follow-up. All statistical analyses were performed with SPSS version 10.0 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

The demographic characteristics and clinical manifestations of sarcoidosis in the 56 patients are shown in Table 2,[7–10] while the organs involved are shown in Table 3.

Demographic characteristics

The study cohort comprised 13 men and 43 women. The mean age at disease onset was 38 years in men, 50 years in women and 47 years (range, 18–76 years) in all patients. Thirty-six patients (64.3%) were aged 40–70 years at disease onset, four (7.1%) were > 70 years old, and 16 (28.6%) were < 40 years old. There was a seasonal variation in disease onset, with a higher incidence

Table 2. Demographic data and clinical manifestations of sarcoidosis patients in this and previously reported series

	This series (n = 56)	Reynolds[7] (n = 67)	Baughman et al[8] (n = 736)	Pietinalho et al[9]		Wang et al[10] (n = 25)
				(n = 245)	(n = 189)	
Female (%)	76.8	59.7	63.6	67.0	60.0	52.0
Country of origin	Taiwan	USA	USA	Japan	Finland	China
Age at presentation < 40 yr (%)	28.6	58.0	54.0	N/A	N/A	40.0
Mean age at onset (yr)	47.0	38.7	36.0	41.5	30.0	47.2
Chest radiograph (%)						
Stage 0	17.8	1.5	8.3	18.0	1.0	12.0
Stage I	53.6	59.0	39.7	57.0	48.0	28.0
Stage II	28.6	32.0	36.7	20.0	39.0	56.0
Stage III	0	0	9.8	5.0	12.0	4.0
Stage IV	0	9.0	5.4	0	0	0
Clinical manifestations (%)						
Pulmonary symptoms	82.1	98.0	95.0	3.0	33.0	88.0
Skin	26.8	36.0	24.2	0	18.0	36.0
Eyes	19.6	9.0	11.8	41.0	5.0	4.0
Arthralgia/arthritis	17.8	13.4	0.5	16.0	16.0	8.0
Hypercalcemia	20.0	18.0	3.7	N/A	N/A	11.0
Heart	1.8	9.0	2.3	N/A	N/A	N/A
Neurologic system	1.8	9.0	4.6	N/A	N/A	N/A
Löfgren's syndrome	3.6	9.0	N/A	N/A	N/A	N/A

N/A = not available.

(66.3%) in winter and early spring, and a lower incidence (18.8%) in autumn.

Clinical presentation

The most common manifestations were respiratory, cutaneous, ocular and articular symptoms (Table 2). There were seven (12.5%) asymptomatic patients, who were identified by routine chest radiography during physical check-up. Three of the 56 patients also had constitutional symptoms, i.e. fever, fatigue and body weight loss.

Pulmonary manifestations

Isolated pulmonary involvement was found in 25 patients (44.6%) (Table 3). Twenty-six (46.4%) patients presented with pulmonary symptoms, including cough, exertional dyspnea and chest tightness. Pulmonary symptoms were associated with extrathoracic manifestations in 24 (42.9%) patients, including joint pain, ocular involvement and cutaneous lesions. The distribution of staging of the chest radiographs is summarized in Table 2. The chest radiographs were normal (stage 0) in 17.8% of patients, stage I in 53.6%, and stage II in 28.6%. Neither stage III nor IV was found on chest radiographs in this series.

Gallium-67 scan

Gallium-67 scan was performed in 40 of the 56 patients. The lambda sign, i.e. increased uptake in the bilateral hilar lymph nodes, was found in 30 (75%) patients, while the panda sign, i.e. increased uptake in the lacrimal glands, was noted in four (10%).

Table 3. Organ involvement in patients with sarcoidosis

Involved organ	*n* (%)
Lung only	25 (44.6)
Lung + skin	7 (12.5)
Lung + skin + joints	6 (10.7)
Lung + joints + eyes	4 (7.1)
Lung + peripheral lymph nodes	4 (7.1)
Eyes only	3 (5.4)
Lung + eyes	3 (5.4)
Skin + eyes	1 (1.8)
Lung + heart	1 (1.8)
Central nervous system	1 (1.8)
Skin only	1 (1.8)

Skin manifestations

Erythema nodosum was the most common cutaneous manifestation. Fifteen of 56 (26.8%) patients had skin lesions, including nine with erythema nodosum in the lower extremities. Six patients presented with erythematous nodular lesions, which developed over the cheeks in five and forehead in one.

Ocular manifestations

Eleven (19.6%) patients had ocular involvement. Among them, eight presented with panuveitis, two with nodular scleritis and one with retinal vasculitis.

Articular manifestations

Ten (17.8%) patients presented with arthralgia or arthritis followed by pulmonary symptoms. The involved joints included the ankle (5 patients), knee (2), both wrists (2) and bilateral proximal interphalangeal joints of the hands (1). No bony destruction was found on radiography in these patients.

Involvement of other organs

Neurosarcoidosis was demonstrated by biopsy of a pituitary mass in one female patient. Another woman presented with first degree atrioventricular block, which progressed to complete atrioventricular block 3 years later. Gallium-67 scan showed increased uptake in the heart, bilateral hilar lymph nodes and lungs in this patient.

Pathologic findings of biopsy specimens

Biopsies of affected organs were performed in 48 of 56 patients. The pathologic findings showed noncaseating epithelioid and giant cell granulomas. The most common sources of positive biopsy specimens were the intrathoracic lymph nodes (39 patients), followed by skin (4) and lung (2). Other sites of positive biopsies included the nodular scleritis (2 patients), extrathoracic lymph

nodes (3), and pituitary gland (1). Forty-six patients (82.1%) had a positive biopsy from a single organ site and five (8.9%) had positive findings from two organ sites.

Laboratory findings

Elevation of serum calcium (> 11 mg/dL) was noted in only six (20%) of 30 patients whose serum calcium data were available. Four of them were asymptomatic and two had symptomatic hypercalcemia (consciousness change), elevated plasma creatinine and nephrocalcinosis.

The mean level of sACE at disease presentation was 26.27 ± 1.59 IU/L (range, 11.8–51.9 IU/L; upper limit of normal, 21.4 IU/L). sACE was elevated in 72.5% (29/40) of patients at disease onset, and declined to within the normal range in 50% (20/40) of patients after remission. Elevation of sACE was significantly greater in patients with lung involvement (stage I and stage II) (27.98 ± 1.71 IU/L vs. 18.2 ± 2.76 IU/L; $p < 0.01$) (Figure 1). No significant difference in sACE level was found between patients with stage I and stage II disease. No significant association of sACE level with age, gender, extrapulmonary manifestations or outcome of treatment was found. In 20 of the 40 patients, sACE level declined significantly after treatment (24.75 ± 1.53 IU/L vs. 16.33 ± 1.21 IU/L; $p < 0.05$) (Figure 2A). Moreover, sACE level paralleled clinical disease activity (Figure 2B).

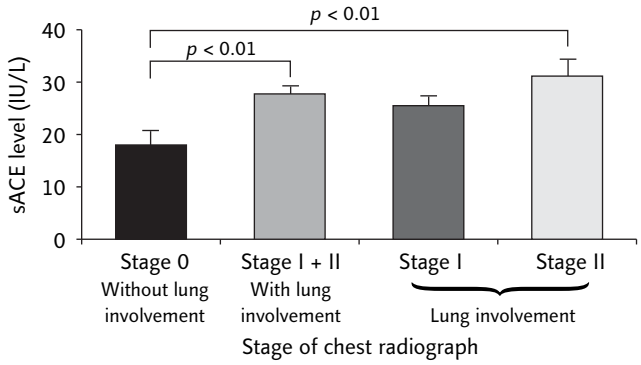

Figure 1. Serum angiotensin converting enzyme (sACE) level in sarcoidosis patients with different clinical stage on chest radiograph. Data are presented as mean ± SEM.

Disease course

Three patients were lost to follow-up. Spontaneous remission occurred in 11 (20.7%) of the remaining 53 patients, and complete remission after treatment with corticosteroid or other immunosuppressive agents, including methotrexate, cyclosporine and cyclophosphamide, occurred in 17 (32.1%) patients (Table 4). Persistent symptoms or bilateral hilar lymphadenopathy on serial chest radiographs was noted in 25 (47.2%) patients.

Discussion

Sarcoidosis is still considered rare in Taiwan, and studies of the relationship among sACE, clinical manifestations and treatment outcome have not

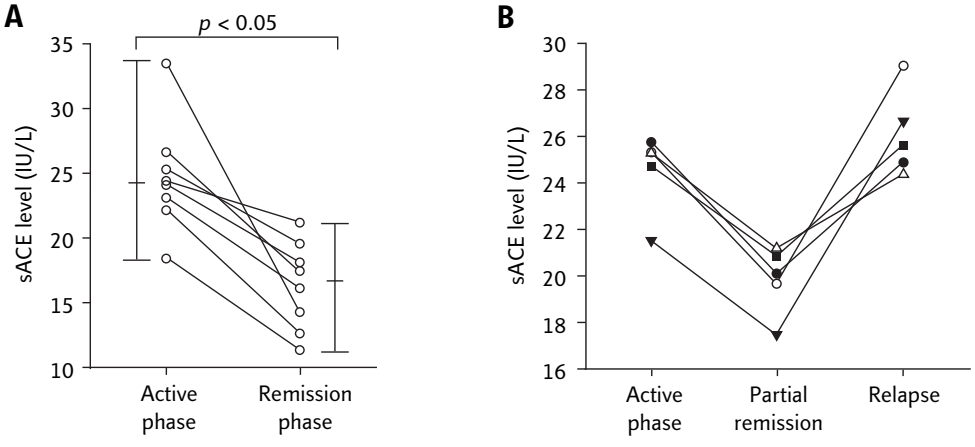

Figure 2. (A) Change in serum angiotensin converting enzyme (sACE) levels in eight sarcoidosis patients from disease onset to remission. The three horizontal lines in each vertical line represent the maximum, median and minimal values, respectively. (B) Serial changes in sACE levels in five sarcoidosis patients in the active phase, partial remission phase and at relapse.

been previously reported. In this study, there was a higher proportion of females (76.8%) (Table 2). The mean age at disease onset was 47 years, which is much older than the mean of 36 years reported in a study of white patients by Baughman et al,[8] but similar to the mean age of 41.5 years in Japanese patients reported by Pietinalho et al,[9] and the 47.2 years in a study of Chinese patients by Wang et al.[10] The Asian population seems to have an older age at disease onset. Analysis of the seasonal differences at disease onset in this study showed a predominance in winter (39.3%) and early spring (21.4%), with minimal occurrence in autumn. This finding is consistent with studies by Newman et al[1] and Bardinas et al.[11] In some small series, different seasonal clusters were reported; 70% of cases in Greece were identified between March and May every year,[6] 50% of diagnoses in Spain were made between April and June,[11] and most cases in Japan occurred during June and July.[12] The difference in seasonal clustering implies that environmental factors may be important in the etiology of the disease.

In this series, the major clinical features included pulmonary symptoms, erythema nodosum, uveitis and arthralgia/arthritis, which are consistent with the previous reports of Perng et al[3] and Baughman et al.[8] However, more ophthalmic (9 females, 2 males) and cutaneous (10 females, 5 males) involvements were noted in females in this study. This is consistent with the finding by Baughman et al that pulmonary and ocular involvement followed by erythema nodosum predominated in a group of female patients in the U.S.[8] The 3.6% incidence of Löfgren's syndrome, i.e. fever, arthritis/arthralgia, hilar adenopathy and erythema nodosum, in this study is lower than the range of 8.4–19.1% in previous reports.[6,13] The majority of our patients (44.6%) presented with isolated pulmonary involvement, followed by pulmonary involvement combined with cutaneous manifestations (12.5%), and pulmonary and cutaneous manifestations with articular involvement (10.7%) (Table 3). None of the patients in this series were in an advanced clinical stage based on chest radiographs, which is similar to findings in a report from China.[10] In contrast, advanced clinical stage was found in 9–15% of white patients.[7,8] The milder pulmonary involvement in this series compared to those series[7,8] suggests that race might be a contributory factor.

About 5–10% of systemic sarcoidosis presented as neurosarcoidosis.[1,14] However, the incidence of isolated neurosarcoidosis was estimated at less than 0.2 per 1,000,000 among whites.[14] In this series, only one female patient presented with isolated central nervous system involvement. This patient had a good response to treatment with steroid and methotrexate. Another female patient developed cardiac sarcoidosis with arrhythmias developing after being free of pulmonary symptoms (stage II) for half a year. Her condition worsened to complete atrioventricular block 3 years later despite aggressive treatment.

The laboratory findings in this series are similar to those reported in previous ones,[1,5,6,8] In sarcoidosis, ACE is produced by epithelioid cells and alveolar macrophages at the periphery of granulomas in response to an ACE-inducing factor released by T-lymphocytes.[15] In this study, sACE was found to be markedly increased in 72.5% of active sarcoidosis patients. Increased levels of ACE

Table 4. Therapeutic agents used in patients with complete remission (n = 28) and persistent/progressive disease (n = 25)

Therapeutic agent	Complete remission, n (%)	Persistent/progressive disease, n (%)
No treatment	11 (20.7)	4 (7.5)
Corticosteroids	11 (20.7)	10 (18.9)
Corticosteroids + methotrexate	6 (11.3)	7 (13.2)
Corticosteroids + other immunosuppressants*	0 (0.0)	4 (7.5)

**Other immunosuppressants = cyclosporine, cyclophosphamide.*

have also been reported in nonsarcoid disorders and are neither pathognomonic nor diagnostic for the disease.[16,17] Shigehara et al reported that sACE correlated well with the serum concentration of interleukin-12, which may be a useful clinical marker of pulmonary sarcoidosis.[18] In this study, significantly higher levels of sACE were found in the active stage than in the remission stage ($p < 0.05$, Figure 2A). Serial measurements of sACE can be used to evaluate therapeutic efficacy and to predict disease recurrence. Moreover, the levels of sACE paralleled clinical disease activity (Figure 2B). Significantly higher levels of sACE were found in patients with lung involvement ($p < 0.01$; Figure 1). Therefore, a higher sACE level in the active stage should lead to suspicion of pulmonary involvement and should also be considered as an indicator for aggressive treatment. However, no significant association was found between sACE and extrapulmonary manifestations or treatment outcome.

Forty of the 56 patients had undergone gallium-67 scan. Seventy-five percent of these patients showed an area of increased uptake in bilateral hilar lymph nodes (lambda sign), and 10% showed increased uptake in the lacrimal glands and parotid glands and/or submandibular glands (panda sign). Sulavik et al found the lambda sign in 79% of sarcoidosis patients and the panda sign in 72%.[19] However, gallium-67 scan had no diagnostic value in sarcoidosis if there were no associated clinical manifestations or pathologic evidence.[18,19]

The disease course and prognosis of sarcoidosis may vary considerably among different geographical regions. The relationship between disease course and prognosis in different countries might be attributable to genetic and environmental factors.[5] In this study, only 20.7% of patients had spontaneous remission, and 32.1% showed remission after treatment with corticosteroid or other immunosuppressive agents (Table 4). Persistent symptoms or bilateral hilar lymphadenopathy on serial chest radiographs was noted in 47.2% of patients. Acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs.[5,20] Complete remission occurred in nearly half of the patients in this study, and this finding is consistent with data in whites.[20] Some studies have found that African-American patients had a higher rate of extrapulmonary involvement, chronic progressive disease, worse long-term prognosis, and higher rate of relapse.[5,21] Patients with extrapulmonary manifestations responded poorly to standard medical treatment.

In conclusion, the clinical features in our patients were similar to those reported in studies of whites, although our patients had lower incidences of Löfgren's syndrome and advanced pulmonary involvement did not occur. Similar to Chinese and Japanese patients with sarcoidosis, the age of disease onset was also older in our patients than in whites. sACE levels, which decreased significantly after corticosteroid treatment with/without immunosuppressants, paralleled clinical remission. Higher sACE levels were found in sarcoid patients with lung involvement. Our results suggest the existence of interethnic differences in clinical manifestation and disease outcome, but a large prospective cohort study including an immunogenetic investigation would be needed to verify this hypothesis.

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