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Abstract

Clinical features were studied in 125 patients with sarcoidosis (72 females and 53 males) diagnosed at Okayama University Hospital during a recent 10-year period. The age distribution had two peaks in patients in their 20s and the 50s. Over half of the patients were detected at health screening check and were asymptomatic, while the remaining were symptomatic. Twelve patients were in stage 0, 41 were in stage I, 54 were in stage II, 16 were in stage III, and 2 were in stage IV according to the chest x-ray findings. Serum angiotensin converting enzyme levels and serum lysozyme levels were elevated in 60% and 76% of the patients, respectively. The bronchoalveolar lavage fluid showed lymphocytosis, especially of helper T-cells. The clinical features of sarcoidosis appear to depend on the duration of the disease.

KEYWORDS: sarcoidosis, serum angiotesin converting enzyme, bronchoalveolar lavage

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Clinical Features of 125 Patients with Sarcoidosis: Okayama University Hospital Review of a Recent 10-Year period

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Clinical features were studied in 125 patients with sarcoidosis (72 females and 53 males) diagnosed at Okayama University Hospital during a recent 10-year period. The age distribution had two peaks in patients in their 20s and the 50s. Over half of the patients were detected at health screening check and were asymptomatic, while the remaining were symptomatic. Twelve patients were in stage 0, 41 were in stage I, 54 were in stage II, 16 were in stage III, and 2 were in stage IV according to the chest x-ray findings. Serum angiotensin converting enzyme levels and serum lysozyme levels were elevated in 60% and 76% of the patients, respectively. The bronchoalveolar lavage fluid showed lymphocytosis, especially of helper T-cells. The clinical features of sarcoidosis appear to depend on the duration of the disease.

Key words : **sarcoidosis, serum angiotensin converting enzyme, bronchoalveolar lavage**

Sarcoidosis is a generalized granulomatous disease of unknown etiology (1), the clinical features of which have gradually been made clear by the investigation of many patients. Recent immunocytological studies, especially those involving bronchoalveolar lavage (BAL) and transbronchial biopsy (TBLB), have greatly improved our understanding of this disease. In Japan, over 7,000 cases of sarcoidosis have been documented in seven nationwide surveys (1960–1984), and the actual status of this disease is becoming clear (2, 3). In this study, we examined the clinical features of 125 patients whom we diagnosed in a recent 10-year period.

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Subjects and Methods

Subjects. One hundred and twenty-five patients, comprising 72 females and 53 males, were diagnosed as having sarcoidosis at Okayama University Hospital between 1978 and 1988. Patient characteristics are shown in Table 1. The age range was from 11 to 79 years (median age; 46 years), and the age distribution showed two peaks at 20–29 and 50–59 years; men showed the former peak, while women showed the latter peak years (Fig. 1). Forty-eight patients were smokers, and 77 were nonsmokers. Biopsy specimens were histologically examined by hematoxylin-eosin stain and verification of the diagnosis of sarcoidosis was obtained in 92 patients, and the diagnosis in the remaining 33 was based on characteristic chest x-ray findings and immunological data (4).

Radiology. Five radiologic stages were distinguished according to the criteria of the Japan Sarcoidosis Committee (5): Stage 0 (a normal chest radiograph), Stage I (bilateral hilar lymphadenopathy), Stage II (bilateral hilar lymphadenopathy and parenchymal infiltration), stage III (parenchymal infiltration), and stage IV (pulmonary fibrosis).

Table 1 Characteristics of the 125 patients with sarcoidosis

Features	Number	%
Female	72	58
Male	53	42
Age > 40	72	58
Chest x-ray		
Stage 0	12	10
Stage I	41	33
Stage II	54	43
Stage III	16	13
Stage IV	2	2
Asymptomatic	52	42
Symptomatic	73	58
Eye	23	18
Cough	16	13
Skin	9	7
Lymphadenopathy	5	4
Dyspnea	5	4
Others	15	12
Biopsy		
TBLB	40/63[a]	63
Scalene node	37/49	76
Skin	26/31	84

TBLB: Transbronchial lung biopsy. *a*: number of patients with diagnostic noncaseating epitheloid granuloma/number of patients examined. Median age (range) of patients studied: 46 (11～79) years.

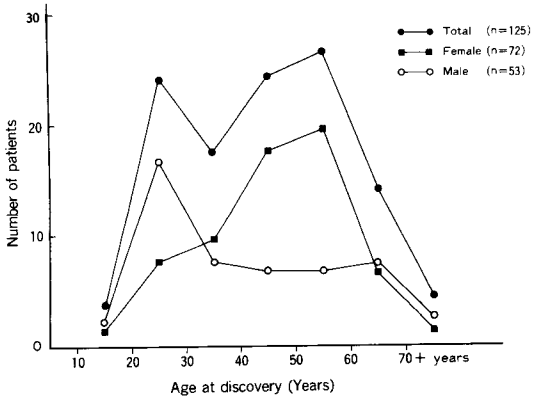

Fig. 1 Age distribution of 125 sarcoidosis patients at diagnosis.

Bronchoalveolar lavage (BAL). Sterile normal saline solution was introduced through a fiberoptic bronchoscope wedged in a segmental or subsegmental bronchus of the right middle lobe. Four subsequent aliquots of 50 ml were instilled and recovered by gentle aspiration. Total cell and differential cell counts in BAL fluid were done, and the lymphocyte subsets, and CD4/CD8 ratio were evaluated using flow cytometry.

Statistical analysis. Data were analyzed by chi-square and Student's *t*-test or non-parametric method for two means. P values less than 0.05 were considered significant.

Results

Incidence of symptoms. Forty-two percent of these patients were discovered to have abnormal chest x-ray findings without any symptoms by routine health screening or mass screening surveys, while 58 % were symptomatic. Ocular symptoms were the most common initial manifestations (18 %). The other symptoms were cough (13 %), skin lesion (7 %), peripheral lymphadenopathy (4 %), dyspnea (4 %), and others (12 %) (Table 1). The organ most often affected was the lung (88 %), and the other affected organs were the eye (38 %), peripheral lymph nodes (30 %), skin (21 %), liver (7 %), spleen (3 %), bone (2 %), salivery gland (2 %), and others (4 %).

Percentage of biopsy specimens showing positive findings for sarcoidosis. The percentages of positive specimens during our 10 year survey were 63 % (40 / 63 patients), 76 % (37 / 49 patients) and 84 % (26 / 31 patients) for TBLB, scalene node biopsy, and skin biopsy, respectively (Table 1). During the former 5 years, TBLB was done only in 9 patients and positive findings were observed in 55 % specimens. During the latter 5 years, TBLB was performed in 54 patients and the rate of positive specimens increased to 68 %.

Chest radiographic stage at diagnosis. At

diagnosis, stage 0 patients accounted for 10 %, stage I for 33 %, stage II for 43 %, stage III for 13 %, and stage IV for 2 % (Table 1). Compared to the results of nationwide surveys by the Japan Sarcoidosis Committee (1), our series had a higher frequency of stage II and stage III.

Laboratory findings. Serum angiotensin converting enzyme (ACE) levels were elevated in 69 of the 119 patients tested (60 %). Serum lysozyme levels were elevated in 76 of the 100 patients (76 %), and serum immunosuppressive acidic protein (IAP) levels were also elevated in 31 of the 92 patients (34 %). Seventy of the 110 patients (64 %) had a negative PPD skin test. On 67-Gallium scintigraphy, 53 of the 80 patients (73 %) showed positive uptake by the hilar lymph nodes and 33 patients (41 %) showed lung field uptake (Table 2).

Analysis of bronchoalveolar fluid. BAL was performed in 94 patients, comprising 57 nonsmokers and 37 smokers, using a fiberoptic bronchoscope. The total number of cells was $19.2 \pm 12.3 \times 10^6$ cells (mean $\pm$ SD) for nonsmokers with sarcoidosis and $30.5 \pm 19.2 \times 10^6$ cells for smokers with sarcoidosis, both being significantly larger than that of healthy nonsmokers ($9.7 \pm 4.3 \times 10^6$ cells, $p < 0.01$) (Fig. 2). The percentage of lymphocytes in BAL fluid was significantly high in patients with sarcoidosis, in both nonsmokers (36.6 ± 22.2 %) and smokers (27.5 ± 23.0 %) compared to healthy nonsmokers (10.9 ± 8.1 %, $p < 0.05$). The absolute number of lymphocytes also significantly increased in both nonsmokers ($7.6 \pm 4.3 \times 10^6$ cells) and smokers ($8.7 \pm 7.0 \times 10^6$ cells) with sarcoidosis compared to healthy nonsmokers ($1.1 \pm 0.8 \times 10^6$ cells, $p < 0.01$). Although there was no difference in the percentage of macrophages among nonsmokers (60.4 ± 21.7 %) or smokers (71.1 ± 23.4 %) with sarcoidosis and healthy nonsmokers (84.7 ± 8.2 %), the absolute number of macrophages found in smokers with sarcoidosis ($21.7 \pm 16.4 \times 10^6$ cells) was significantly larger than in nonsmokers with sarcoidosis ($11.8 \pm 7.5 \times 10^6$ cells, $p < 0.05$) and healthy nonsmokers ($8.2 \pm 4.0 \times 10^6$ cells $p < 0.05$). The results of lymphocyte subset analysis of BAL fluid are shown in Table 3. There were no significant differences in the percentage of CD3-positive lymphocytes between healthy nonsmokers and nonsmokers or smokers with sarcoidosis. However, both nonsmokers and smokers with sarcoidosis had a significantly higher percentage of CD4-positive lymphocytes ($p < 0.01$) and showed a higher CD4/CD8 ratio than the healthy non-

Table 2 Results of laboratory investigations

Parameters tested	
Serum ACE elevated (> 21.4 U)[a]	69/116 (60 %)[b]
Serum lysozyme elevated (> 10.2 μg/ml)	76/100 (76 %)
Serum IAP elevated (> 500 μg/ml)	31/ 92 (34 %)
PPD skin test negative	70/110 (64 %)
67-Gallium scintigraphy :	
Positive uptake in hilar nodes	58/ 80 (73 %)
in lung fields	33/ 80 (41 %)

ACE: Angiotensin converting enzyme. IAP: Immunosuppressive acidic protein. *a*: Abnormal values are shown in parentheses. *b*: Patient numbers with this finding/patient numbers examined.

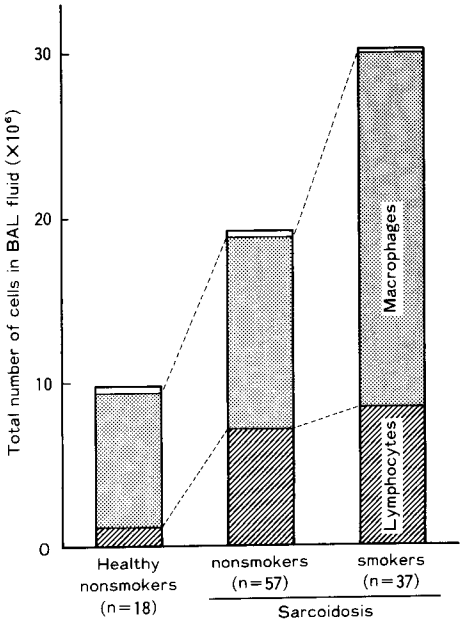

Fig. 2 Total number and proportion of cells present in bronchoalveolar lavage fluid from healthy nonsmokers, nonsmokers with sarcoidosis, and smokers with sarcoidosis.

Table 3 Lymphocyte subsets in bronchoalveolar lavage fluid

	Healthy nonsmokers	Sarcoidosis	
		Nonsmokers	Smokers
Number of subjects	8	36	27
CD3 positive (%)	83.9 ± 9.4	86.5 ± 8.5	87.4 ± 7.3
CD4 positive (%)	56.9 ± 8.2	70.8 ± 11.3*	70.5 ± 12.9*
CD8 positive (%)	32.1 ± 9.0	17.0 ± 8.0*	21.9 ± 12.4*
CD4/CD8 ratio	1.9 ± 0.6	5.5 ± 3.4*	4.5 ± 2.7**

All results are given as the mean ± SD. Significant difference compared to healthy nonsmokers (*: $p < 0.01$, **: $p < 0.02$)

Table 4 A comparison of the clinical disease pattern between the recent onset group and the long-term follow-up group

	Recent onset group	Long-term follow-up group
Number of subjects	10	8
Serum ACE (U)	25.8 ± 5.4	26.2 ± 11.4
Serum lysozyme	19.1 ± 6.1	15.5 ± 6.9
Pulmonary function:		
%VC	94.2 ± 17.8*	68.4 ± 20.6
FEV 1.0%	86.5 ± 7.8	81.2 ± 3.3
%DLCO	79.0 ± 16.9	64.5 ± 25.6
67-Gallium Scintigraphy:		
Hilar nodes positive	8/9*	2/6
Lung fields positive	4/9	5/6
BAL findings		
Total cell count ($\times 10^6$)	27.7 ± 11.7	19.1 ± 13.1
Macrophages ($\times 10^4$/ml)	13.7 ± 9.1	17.4 ± 14.2
Lymphocytes ($\times 10^4$/ml)	11.2 ± 9.4**	2.7 ± 2.1
CD3 positive (%)	89.7 ± 4.8	92.2 ± 3.2
CD4 positive (%)	78.0 ± 4.4	71.0 ± 9.8
CD8 positive (%)	16.0 ± 3.7	19.9 ± 10.3
CD4/CD8 ratio	5.3 ± 2.2	4.6 ± 1.9

All results are given as the mean ± SD. ACE: Angiotensin converting enzyme. BAL: Bronchoalveolar lavage. DLCO: Pulmonary diffusing capacity for carbon monoxide. FEV: Forced expiratory volume. VC: Vital capacity. Significant differences between the recent onset group and the long-term follow-up group (*: $p < 0.05$, **: $p < 0.02$).

smokers ($p < 0.02$). In contrast, the percentage of CD8-positive lymphocytes in sarcoidosis patients was significantly lower than in healthy nonsmokers ($p < 0.01$). There was no significant difference in the percentage of lymphocytes as well as lymphocyte subpopulations in BAL fluid among different chest x-ray stages.

Influence of time since the disease onset on clinical features. We compared 10 patients who had been diagnosed in the past one year (recent onset group) with 8 patients who had been followed up for over 5 years since the onset of their disease (long-term follow-up group) (Table 4). There were no differences between the two groups in serum ACE and lysozyme levels, but in pulmonary function tests, the long-term follow-up group had a significantly lower percent vital capacity (% VC) than the recent onset group ($p < 0.05$). On 67-Gallium scintigraphy, 8 of the 9 patients in the recent onset group showed positive uptake by the hilar lymph nodes, and the rate of positivity was significantly higher than that of the long-term follow-up group ($p < 0.05$). Lymphocytes in BAL fluid in the recent onset group was significantly more than in the long-term follow-up group ($p < 0.02$), but there were no differences in lymphocyte subsets or the CD4/CD8 ratio.

Discussion

The prevalence of sarcoidosis is increasing in Japan (3), and we experienced 125 cases in the last 10 years. The clinical features of our cases were assessed using laboratory tests, radiological studies (chest x-ray and 67-Gallium scintigraphy), and pulmonary function tests. The sex distribution of our cases (F/M: 1.4) was very similar to the results of a nationwide survey in Japan (3). The age distribution of our cases had two peaks in the 20s and the 50s, being different from the

data of the nationwide surveys in Japan (3) and large scale surveys in England (6, 7), which showed one peak at 20–39 years of age. Fifty-eight percent of the patients in our series were over 40 years of age. Patients presenting eye symptoms were more common compared to the series in other countries (6–8). Otherwise, the proportions of the affected organs corresponded well to the other reports (9, 10) although peripheral lymphadenopathy and skin lesions were slightly less common. To obtain the histological verification, TBLB was performed in 50 % of the patients, and scalene node biopsy in 39 %. During the latter 5 years, TBLB was performed in almost all patients, and the rate of positive specimens reached to 68 %, which is lower than the rate given in other reports (75–90 %) (11–13). This suggests some room for improvement in the technique. Elevation of serum ACE levels was seen in 60 % of the patients, corresponding to the report of Lieberman *et al.* (14). Serum lysozyme elevation was seen in over 70 % of our patients, but the disease specificity of lysozyme was lower than that of ACE. The PPD skin test was negative in 64 % of the patients, which corresponds closely to the level in other reports (15, 16). Chest x-ray showed abnormalities of the lung fields (stage II, stage III and stage IV) in 58 % of the patients, while the uptake by the lung fields was noted in only 26 % on 67-Gallium scintigrams. This finding emphasizes that 67-Gallium scintigraphy is less sensitive for detecting granulomatous lesions of the lung field compared to chest x-ray (17). In the BAL fluid, the number of lymphocytes, especially of helper T cells was significantly increased in sarcoidosis compared to healthy nonsmokers, which corresponds to the rsults reported by others (18, 19). This phenomenon was seen in both nonsmokers and smokers with the disease. We compared two groups of sarcoidosis patients, a recent onset group and a group followed up for over 5 years from the onset of disease. Our findings suggested that BAL fluid lymphocytosis, especially of helper T cells, may be the first pathological change in sarcoidosis, perhaps reflecting T cell alveolitis of the lungs. This change is found at the onset and becomes less marked as time goes by. In contrast, pulmonary function tests, especially the % VC, showed progressive impairment and the rate of 67-Gallium uptake by the lung fields becomes higher. The time since the onset thus seems to have a major influence on the presentation of sarcoidosis.

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