

INCIDENCE AND BASELINE CHARACTERISTICS OF RELAPSE OR EXACERBATION IN PATIENTS WITH PULMONARY SARCOIDOSIS IN JAPAN

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ABSTRACT. Background: To identify the incidence and baseline characteristics of relapse and exacerbation in patients with pulmonary sarcoidosis over a long-term period. **Methods:** We enrolled 103 patients. The incidence and characteristics of relapse or exacerbation were retrospectively recorded and statistically analysed. **Results:** Of 103 patients, 79% were women. Mean age at diagnosis was 50.1 ± 16.4 y. Mean observation period was 9.8 ± 8.6 y. Overall relapse or exacerbation was 22.3% ($n = 23$) and mean time from diagnosis (including diagnosis of ocular disease at another facility) to relapse or exacerbation was 8.7 ± 8.3 y. We analysed the data of 69 patients who were observed for > 5 y and identified relapse or exacerbation within 5 y in 9 patients. Comparison of characteristics at diagnosis between the relapse/exacerbation group and the improved/stable group showed that the relapse/exacerbation group had a significantly higher frequency of bilateral hilar lymphadenopathy, longer disease duration, ocular involvement, cardiac involvement, and oral glucocorticoid use at diagnosis ($P = 0.014, 0.027, 0.019, 0.035,$ and 0.0043 , respectively). The number of risk factors was positively and significantly associated with the cumulative rate of relapse/exacerbation ($P = 0.048$). **Conclusion:** Our long-term observational cohort study newly identified the incidence and baseline risk factors for relapse or exacerbation in patients with pulmonary sarcoidosis over a long-term period. Scoring the number of factors at baseline may facilitate the prediction of relapse or exacerbation.

KEY WORDS: Pulmonary sarcoidosis, Prognosis, Risk factor, Long-term observation, Radiography

INTRODUCTION

Sarcoidosis, a systemic granulomatous disease that involves multiple organs, commonly affects young and middle-aged adults and usually presents with pulmonary abnormalities and lymphadenopathy. Spontaneous remission occurs in two-thirds of

patients, while chronic or progressive disease affects 10% to 30% (1). Lung involvement is particularly common, occurring in $> 90\%$ of patients (2), and spontaneous remission of pulmonary sarcoidosis is often observed within 2 years (3). Factors reported to indicate a poor prognosis in pulmonary sarcoidosis include an advanced chest radiographic stage, skin involvement, age > 40 y at presentation, and a smoking history (4, 5). To date, however, few studies have comprehensively described the risk factors for relapse and exacerbation and the outcomes over a long-term period of > 2 y in patients with pulmonary sarcoidosis.

In this study, we investigated the risk factors for relapse and exacerbation in patients with pulmonary sarcoidosis for > 5 y.

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METHODS

Patients

In this retrospective long-term cohort study, we enrolled 103 patients who visited the Department of Pulmonary Medicine of Hachinohe Red Cross Hospital between January 2007 and December 2016 and were clinically diagnosed with pulmonary sarcoidosis. Among 103 patients, to analysis of cumulative rate of relapse or exacerbation, we excluded cases with oral GC use at presentation to avoid influence by treatment, and selected cases who were observed for > 5 y. Then, the data of 69 patients were selected for further analysis.

All procedures were approved by the medical ethics committee of Hachinohe Red Cross Hospital and followed the tenets of the Declaration of Helsinki.

Variables of analysis

We assessed variables which were epidemiology, lung imaging, involved organ other than lung, and laboratory findings suggesting characteristics of sarcoidosis.

Definition of chest radiographic staging of pulmonary sarcoidosis

To improve analytical accuracy, chest X-rays and axial images of chest computed tomography (CT) scans were quantitatively interpreted and were assessed by two observers according to modified criteria based on the stage of pulmonary sarcoidosis by a five-point scale (stage 0–IV) according to the American Thoracic Society statement (1), as follows: “stage 0, no visible intrathoracic findings; stage I, bilateral hilar lymphadenopathy (BHL) only; stage II, bilateral hilar adenopathy accompanied by parenchymal infiltration; stage III, parenchymal infiltration without hilar adenopathy”; and “stage IV, advanced fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts, and emphysema.”

Assessment of lung images

Chest X-rays and Chest CT scans were assessed by two observers who were blinded to the patient's clinical information.

Definition of disease states

We defined the disease states of pulmonary sarcoidosis as follows: “relapse” was the reappearance of former signs or symptoms associated with pulmonary sarcoidosis after remission, such as BHL or parenchymal infiltration on chest X-rays or chest CT scans, or appearance of dyspnea or dry cough; “exacerbation” was the sudden worsening of stable disease, such as BHL, parenchymal infiltration or fibrosis on chest X-rays or chest CT scans, or increased frequency of dyspnea or dry cough; “improved,” was amelioration of signs or symptoms associated with pulmonary sarcoidosis; and “stable,” was neither “relapse,” “exacerbation” nor “improved.”

Statistical analysis

The association of predictive factors for relapse or exacerbation with clinical, laboratory, and radiographic data was analysed by Fisher's exact test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test. Results with $P < 0.05$ were regarded as significant. All statistical analyses were performed with JMP software v. 13.2.1 (SAS Institute Inc., Cary NC, USA).

RESULTS

Clinical characteristics

Clinical characteristics of the 103 patients are listed in Table 1. Mean age at diagnosis was 50.1 ± 16.4 y and 79% were women. Mean observation period was 9.8 ± 8.6 y. The number of patients with previously reported prognostic factors was as follows: chest radiography stage (Stage 0, $n = 7$; Stage I, $n = 32$; Stage II, $n = 36$; Stage III, $n = 18$; and Stage IV, $n = 10$); skin involvement, $n = 9$; age > 40 y, $n = 73$; and smoking history, $n = 38$. Most patients had pulmonary involvement. A total of 69.9% of all patients in this series had extrathoracic manifestations, such as ocular disease. Oral glucocorticoids (GC) were used in one-third of the patients. No drugs other than GC were used in any patient.

Disease relapse or exacerbation

We next focused on disease relapse or exacerbation. Overall relapse or exacerbation rate was 22.3% ($n = 23$) and the mean interval from diagnosis to

Table 1. Clinical characteristics of 103 patients with pulmonary sarcoidosis

Variable	Total (n = 103)
Female, % (n)	78.6 (81)
Mean age, y	50.1 ± 16.4
Observation period, y	9.8 ± 8.6
Smoking, % (n)	36.9 (38)
Mean smoking pack-years (n)	53.0 ± 110.2 (38)
BHL, % (n)	72.8 (75)
Stage 0, % (n)	6.8 (7)
Stage I, % (n)	30.1 (31)
Stage II, % (n)	35.0 (36)
Stage III, % (n)	18.4 (19)
Stage IV, % (n)	9.7 (10)
Thoracic disease, % (n)	93.2 (96)
Extrathoracic disease, % (n)	69.9 (72)
Ocular disease, % (n)	57.3 (59)
Cardiac disease, % (n)	7.8 (8)
Skin disease, % (n)	8.7 (9)
Exocrine disease, % (n)	3.9 (4)
CNS disease, % (n)	2.9 (3)
Other, % (n)	3.9 (4)
Oral glucocorticoid use, % (n)	35.0 (36)
Relapse or exacerbation, % (n)	22.3 (23)
Improvement, % (n)	22.3 (23)
Stable disease, % (n)	55.3 (57)

BHL: bilateral hilar lymphadenopathy. Data represent the median (IQR), mean ± SD or % (number). Observation period was calculated from the time of diagnosis to the point of last follow-up between January 2007 and December 2016.

relapse or exacerbation was 8.7 ± 8.3 years. Among 103 patients, the data of 69 patients who were observed for > 5 y were selected for further analysis. Of the 69 patients, relapse or exacerbation within 5 years was seen in 9 patients. To identify long-term prognostic factors for relapse or exacerbation in the 69 patients, we divided them into two groups and evaluated the clinical significance of risk factors for relapse or exacerbation. Table 2 shows the disease manifestations in the relapse/exacerbation group. The number of risk factors was positively and significantly associated with the cumulative rate of relapse or exacerbation ($P = 0.022$), as shown in Figure 1.

DISCUSSION

In this study, we found that the relapse or exacerbation rate in patients with pulmonary sarcoidosis was 22.3% in overall analysis and 13% in patients with long-term follow up. Rates of BHL, short disease duration, ocular involvement, cardiac involvement, and oral GC use at diagnosis were significantly elevated in the relapse or exacerbation group. The number of risk factors was positively and significantly associated with the cumulative ratio of relapse or exacerbation.

In a study by Rizzato et al., although disease relapse in patients with spontaneous remission was only 8%, 37–74% of treated patients had an exacerbation or relapse when corticosteroids were tapered or discontinued (6). Regarding pulmonary sarcoidosis, 13–75% of patients with pulmonary sarcoidosis

Table 2. Long-term prognostic factors for relapse or exacerbation in 69 patients with pulmonary sarcoidosis

Variable	Total (n = 69)	Relapse or exacerbation		P
		(-) (n = 60)	(+) (n = 9)	
Female, % (n)	79.7 (55)	78.3 (47)	88.9 (8)	0.44
Mean age, y	49.1 ± 16.3	49.7 ± 16.4	45.2 ± 15.9	0.38
Age ≥ 40 y % (n)	69.6 (48)	71.7 (43)	55.6 (5)	0.34
Disease duration, y	9.8 (6.9–18.9)	14.2 ± 8.5	7.6 ± 1.9	0.027
Smoking, % (n)	34.8 (24)	33.3 (20)	44.4 (4)	0.52
Mean smoking pack-years (n)	60.7 ± 133.5 (24)	42.3 ± 73.4 (20)	152.8 ± 298.2 (4)	0.82
Histological diagnosis, % (n)	52.3 (34/65)	48.2 (27/56)	77.8 (7)	0.086
ACE ≥ 21.4 U/l, % (n)	52.5 (31/59)	50.0 (25/50)	66.7 (6)	0.35
ACE, U/l (n)	23.1 (15.4–30.7) (59)	23.7 ± 11.2 (50)	26.7 ± 12.0 (9)	0.59
Lysozyme ≥ 10.2 mg/l, % (n)	55.6 (20/36)	54.8 (17/31)	60.0 (3/5)	0.83

Table 2 (continued)

Variable	Total (n = 69)	Relapse or exacerbation		P
		(-) (n = 60)	(+) (n = 9)	
Lysozyme, mg/l (n)	10.5 (7.3–16.1) (36)	12.8 ± 8.5 (31)	21.5 ± 26.6 (5)	0.72
sIL-2R ≥ 519 U/ml, % (n)	85.7 (12/14)	81.8 (9/11)	100 (3/3)	0.31
sIL-2R, U/ml (n)	859 (556–1420) (14)	970.3 ± 509.0 (11)	1164.3 ± 975.5 (3)	0.94
Ca, nmon/l (n)	2.4 (2.3–2.4) (42)	2.4 ± 0.4 (35)	2.4 ± 0.1 (7)	0.61
Serum Lym, /μl (n)	1220 (988–1661) (54)	1357 ± 471 (46)	1114 ± 495 (6)	0.13
BALF Lym ≥17%, % (n)	72.3 (34/47)	71.1 (27/38)	77.8 (7/9)	0.68
BALF Lym, % (n)	23.3 (11.4–42.5) (47)	29.1 ± 24.6 (38)	32.2 ± 25.8 (9)	0.76
BALF CD4/CD8 >3.5, % (n)	68.8 (33/48)	74.4 (29/39)	44.4 (4/9)	0.091
BALF CD4/CD8 (n)	4.7 (2.7–6.9) (48)	5.2 ± 2.6 (39)	4.3 ± 2.7 (9)	0.26
BHL, % (n)	72.5 (50)	68.3 (41/60)	100 (9)	0.012*
Stage 0, % (n)	5.8 (4)	6.7 (4)	0 (0)	
Stage I, % (n)	29.0 (20)	26.7 (16)	44.4 (4)	
Stage II, % (n)	37.7 (26)	35.0 (21)	55.6 (5)	0.09
Stage III, % (n)	18.8 (13)	21.7 (13)	0 (0)	
Stage IV, % (n)	8.7 (6)	10.0 (6)	0 (0)	
Intrathoracic disease, % (n)	94.2 (65)	93.3 (56)	100 (9)	
Extrathoracic disease, % (n)	66.7 (46)	63.3 (38)	88.9 (8)	0.10
Ocular disease, % (n)	55.1 (38)	50.0 (30)	88.9 (8)	0.019*
Cardiac disease, % (n)	10.1 (7)	6.7 (4)	33.3 (3)	0.035*
Skin, % (n)	7.3 (5)	6.7 (4)	11.1 (1)	0.65
Exocrine, % (n)	4.4 (3)	5.0 (3)	0 (0)	0.35
CNS disease, % (n)	0 (0)	0 (0)	0 (0)	NA
Others, % (n)	4.4 (3)	5.0 (3)	0 (0)	0.35
Oral glucocorticoid use, % (n)	37.7 (26)	33.3 (20)	66.7 (6)	0.058
Glucocorticoid begun at diagnosis, % (n)	17.4 (12)	11.7 (7)	55.6 (5)	0.0043**

*: $P < 0.05$, **: $P < 0.01$, BHL: bilateral hilar lymphadenopathy, ACE: angiotensin converting enzyme, sIL-2R: soluble Interleukin 2 receptor, BALF: bronchoalveolar lavage fluid, NA: not applicable. Data represented the median (IQR), the mean ± SD or % (number). P was calculated using Fisher's exact test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test. Disease duration was calculated on the basis of the period from the time of diagnosis to the time of the first relapse/exacerbation of pulmonary sarcoidosis or the point of last follow-up between January 2007 and December 2016.

progressed (6–9). In our present study, the prevalence of progression was 22.3%, similar to that in a previous report (10), even though this study included both treated and untreated patients since the time of diagnosis.

The proportion of patients who received therapeutic intervention such as

GC was 35.0%, a similar level to that in previous reports (30%–50%) (1). Generally, asymptomatic pulmonary sarcoidosis patients are not treated. In most cases, an indication for treatment would be determined carefully at the time of initial diagnosis (11). In this study, 55.6% of patients in the relapse/

exacerbation group were receiving GC therapy at the time of initial diagnosis. We speculated that certain patients in the relapse/exacerbation group would have had reason to start treatment for symptoms in any target organ. We cannot call GC treatment a negative prognostic predictor.

Longer disease duration has been reported as a risk factor for progression of sarcoidosis (12). In our analysis, in contrast, a shorter disease duration was extracted as a risk factor. We speculate that the presence of more patients with recent onset in the relapse/exacerbation group may have affected our results. A previous study reported that mediastinal

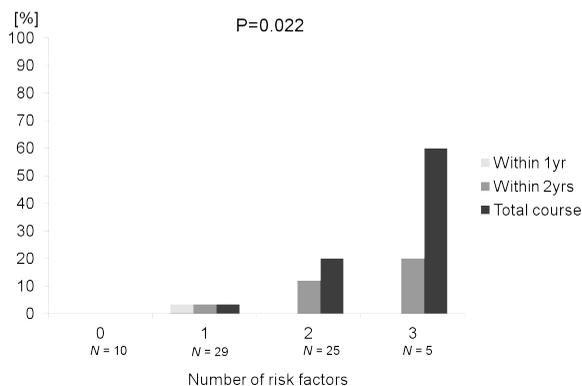


Figure 1. Cumulative rate of relapse or exacerbation in 69 patients with pulmonary sarcoidosis. Positivity of three risk factors, namely bilateral hilar lymphadenopathy, ocular involvement, and cardiac involvement except oral glucocorticoid use at diagnosis and short disease duration were counted. *P* values were calculated using the Kruskal-Wallis test.

lymphadenopathy on chest radiography was associated with a favourable outcome in a previous report (13). In our study, in contrast, BHL was extracted as a risk factor. We speculate that the presence of only Stage I or II cases in the relapse/exacerbation group may have affected our results. In addition, early GC intervention was provided to the patients in an advanced stage at diagnosis. Chronic uveitis and cardiac involvement are known as poor prognostic factors (14, 15). We obtained similar results in our analysis.

This study is subject to limitations. First, it was a single-centre retrospective cohort study and more than half of the patients in the relapse/exacerbation group had already been treated following diagnosis. Thus, we cannot exclude the effect of treatment on relapse or exacerbation. Second, we mainly evaluated chest CT scans, and might therefore have been unable to detect relapse or exacerbation of extrathoracic disease, such as the uveae and heart.

In conclusion, this long-term, single centre retrospective cohort study revealed the incidence and baseline characteristics associated with relapse or exacerbation in patients with pulmonary sarcoidosis not taking GC. Further, the study showed that the cumulative ratio of relapse or exacerbation varied according to the number of risk factors. The number of risk factors may help to predict long-term prognosis. Patients with these factors, particularly those with three risk factors, may need careful observation for appropriate management of disease.

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Ethics: All procedures were approved by the medical ethics committee of Hachinohe Red Cross Hospital and followed the tenets of the Declaration of Helsinki.

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