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Clinical significance of the "galaxy sign" in patients with pulmonary sarcoidosis in a Japanese single-center cohort

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Abstract. *Background:* The galaxy sign is an irregularly marginated pulmonary nodule formed by a confluence of multiple small nodules, and it is a diagnostic radiological finding for pulmonary sarcoidosis. However, the clinical significance of the galaxy sign for sarcoidosis has been poorly investigated. *Objective:* This study aimed to investigate the clinical significance and detailed radiological features of the galaxy sign in patients with pulmonary sarcoidosis. *Methods:* We retrospectively reviewed 87 patients with biopsy-proven sarcoidosis and 108 patients with pulmonary tuberculosis. Galaxy sign incidence was assessed on thoracic high-resolution computed tomography (HRCT) images from each group. Correlations of galaxy sign with clinical characteristics and disease outcomes were evaluated for patients with sarcoidosis. *Results:* HRCT findings were available for 65 of 87 patients with pulmonary sarcoidosis and all 108 patients with pulmonary tuberculosis. Galaxy sign incidence was significantly higher in patients with pulmonary sarcoidosis (n=15, 23.1%) than in those with pulmonary tuberculosis (n=2, 1.9%, $p<0.001$). Among the 65 patients with pulmonary sarcoidosis, those with galaxy signs (n=15) were significantly younger (median: 32 years, interquartile range [IQR] 28-38 years) than those without (n=50) (median: 62 years, IQR 37.7-73 years). The CD4/CD8 ratio in bronchoalveolar lavage fluid (BALF) was also significantly lower in the former group (median: 2.6, IQR 2.0-3.9 vs. median 5.8, IQR 3.7-8.6, $p<0.001$). *Conclusion:* Galaxy signs are associated with younger age and low BALF CD4/CD8 ratio but not disease severity. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 247-252)*

Key words: pulmonary sarcoidosis, galaxy sign, clinical significance

Introduction

The galaxy sign was first described by Nakatsu et al. in 16 of 59 patients (27%) with histologically confirmed sarcoidosis in 2002. This sign was defined as 1) nodules with irregular margins consisting of numerous small nodules with relatively distinct margins, and 2) low attenuation areas in the nodules (1). Previous reports have demonstrated that galaxy signs are also present in patients with active pulmo-

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nary tuberculosis, lung cancer, and progressive massive fibrosis (1, 2). However, no previous report has described the clinical significance of the galaxy sign or radiological features (i.e., size and distribution) associated with it. Thus, in this study, we aimed to clarify the clinical significance of galaxy signs in a cross-sectional study.

Material and Methods

Setting and Study Design

We retrospectively reviewed the medical records and radiology findings of 87 consecutive patients with biopsy proven sarcoidosis, followed up in our hospital from January 2006 to October 2014. This retrospective study was approved by the Ethics Board of Kyorin University (Mitaka, Tokyo, Japan; approval number: H26-123). To examine galaxy sign specificity, sign incidence was also assessed in 108 patients with microbiologically confirmed active pulmonary tuberculosis. Two pulmonologists and one radiologist with at least 10 years of experience independently reviewed high-resolution computed tomography (HRCT) findings, and their decisions were interpreted by consensus. Interobserver correlation scores among the three reviewers were as follows: S.T and Y.T, κ=0.733; H.I and Y.T, κ=0.607; and S.T and H.I, κ=0.467.

Clinical relevance of galaxy signs

The definition for galaxy sign was modified from the criteria by Nakatsu et al. (1) (Fig. 1). Our definition included that the cluster of small nodules should be larger than 10 mm in a diameter. Therefore, the modified galaxy sign criteria (Fig. 1) were as follows 1) nodules larger than 10 mm in size, 2) nodules consisting of numerous small nodules, 3) irregular margins, 4) constituent small nodules that each had relatively distinct margins, and 5) a low attenuation area in the nodule.

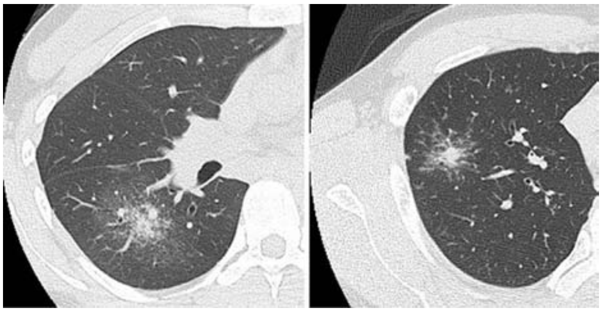

Fig. 1. Representative galaxy sign images. High-resolution computed tomography shows nodules with irregular borders (arrows), which were composed of numerous small nodules with relatively distinct margins and contained a low attenuation area, known as the galaxy sign

Correlations between the galaxy sign and clinical findings, such as steroid use, advent of neurological or cardiac involvement, number of involved organs, proportion of smokers (ex or current), laboratory data, and bronchoalveolar lavage fluid (BALF) findings were assessed.

Radiological assessment on high-resolution computed tomography (HRCT)

Galaxy signs were analyzed according to number, size, and location in horizontal (either right or left thorax) or vertical (upper, middle, and lower lung fields) aspects (Fig. 2). The upper field was defined as the portion of the lung above the tracheal carina, whereas the lower field was defined as the portion of the lung below the inferior pulmonary vein. The middle field was defined as the portion of the lung between the upper and lower zones.

Statistical analyses

Data were statistically analyzed by Pearson's χ^2 test or the Mann-Whitney *U*-test using SPSS ver-

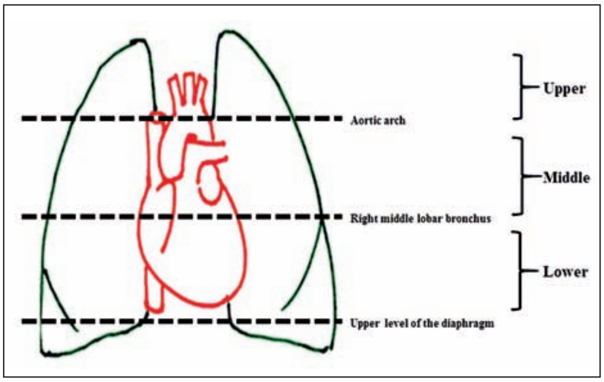

Fig. 2. Visual scoring system. Vertical analysis was performed by dividing lungs into upper, middle, and lower lung fields. The upper zone was defined as the portion of the lung above the tracheal carina, whereas the lower zone was defined as the portion of the lung below the inferior pulmonary vein. The middle zone was defined as the portion of the lung between the upper and lower zones

sion 22. Statistical significance was defined as a *p* value less than 0.05 by paired two-sided tests.

Results

We retrospectively studied 87 patients with sarcoidosis and 108 patients with active pulmonary tuberculosis. A total of 65 patients had biopsy-proven pulmonary sarcoidosis. Patient demographic and clinical characteristics are shown in Table 1.

Galaxy sign incidence in the pulmonary sarcoidosis and pulmonary tuberculosis groups

The galaxy sign incidence was significantly higher in patients with sarcoidosis (n=15, 23.1%, $p<0.001$) compared to those with tuberculosis (n=2, 1.9%). Among the total of 108 patients with pulmonary tuberculous, 34 patients were positive for acid-fast bacilli staining in the samples obtained from sputum (n=21), gastric acid (n=1), and bronchial washing fluid (n=12). Regarding with the 2 Galaxy positive patients who had pulmonary tuberculosis, the results of acid-fast bacilli staining were negative. The sensitivity and specificity of the galaxy sign for pulmonary sarcoidosis diagnosis were 23.1% and 98.1%, respectively, with an area under the curve of 0.606.

Clinical significance of the galaxy sign

For the 65 patients with pulmonary sarcoidosis, comparisons of clinical features between those with galaxy signs (n=15, 23.1%) and those without galaxy signs (n=50, 76.9%) are shown in Table 1. The male to female ratio was similar in both groups, and the age of former group (median; 32 years, IQR 28-38 years) was significantly younger than that of latter group (median; 62 years, IQR 37.7-73 years, $p<0.001$). Among all 65 patients, the proportion of two-organ involvement was largest in both the galaxy positive and negative groups. The most common combination was combined lung and ocular involvement, both in the galaxy positive (n=6, 40%) and negative groups (n=18, 36%). Regarding the number of involved organs, neither cardiac sarcoidosis, peripheral neuropathy, the proportion of smokers (ex or current), nor steroid use was significantly different between the galaxy sign positive and negative groups (Table 1).

With regard to the distribution of the sarcoidosis chest x-ray staging, no correlation was observed between the galaxy sign positive and negative groups. Serum data (angiotensin converting enzyme, soluble Interleukin-2 receptor, and calcium levels) and bronchoalvelar lavage fluid (BALF) findings at the time of diagnosis were comparable between the galaxy sign positive and negative groups, except for a

Table 1. Demographics and clinical characteristics of patients with sarcoidosis according to galaxy sign positivity or negativity

	Galaxy sign-negative group n=50 (%)	Galaxy sign-positive group n=15 (%)	Total n=65	*p* value
Age (median, IQR)	62 (37.7-73.0)	32 (28-38)	56 (33-71)	<0.001
Sex (M/F)	18/32	8/7	26/39	N.S
2 organs*	25 (50)	8 (53.3)		N.S
3 organs*	15 (30)	4 (26.7)		N.S
4 organs*	2 (4)	1 (6.7)		N.S
Cardiac sarcoidosis	2 (4)	3 (20)		N.S
Smoking	26 (52)	12 (80)		N.S
Steroid	10 (20)	5 (33.3)		N.S
Neuropathy	1 (2)	1 (2)		N.S
Stage				
0	2 (4)	0 (0)		N.S
1	17 (34)	2 (13.3)		N.S
2	26 (52)	10 (66.7)		N.S
3	4 (8)		3 (20)	N.S
4	1 (2)		0 (0)	N.S

*the number of organs involved including the lungs, NA: not available,
IQR: interquartile range

lower CD4/CD8 ratio in the BALF (n=7, median 2.6, IQR 2.0-3.9; Table 2) for the positive group, compared to the negative group (n=33, median 5.8, IQR 3.7-8.6, p=0.001). Similarly, the proportion of the patients who had BALF CD4/CD8 ratios ≥3.5 was significantly lower in the galaxy sign-positive group (n=2, 28.6%) compared to the negative group (n=26, 78.8%, p<0.001). There were no differences in smoking rate (n=6, 85.7% in the galaxy sign-positive group vs. n=19, 61.2% in the galaxy sign-negative group) or gender between groups. Pulmonary function tests did not differ between galaxy sign-positive (n=5) and negative (n=18) patients (Table 2).

Radiological analysis and numbers of galaxy signs

There were 89 total galaxy signs, with a range of 1 to 18 nodules per patient (Fig. 3), and the median nodule number was 3.0 per patient.

Galaxy sign size

Galaxy nodule size ranged from 10 to 60 mm, and no statistical difference was found between the right hemithorax (median 16.5, IQR 14-23.0) and left hemithorax (median 18.0, IQR 14.5-23.0). Galaxy sign sizes were equal in the upper (median: 16.5 mm, IQR 13-25 mm), middle (median: 18.0 mm, IQR 15.0-23.0 mm), and lower lung fields (median: 19.5 mm, IQR 13.8-24.5).

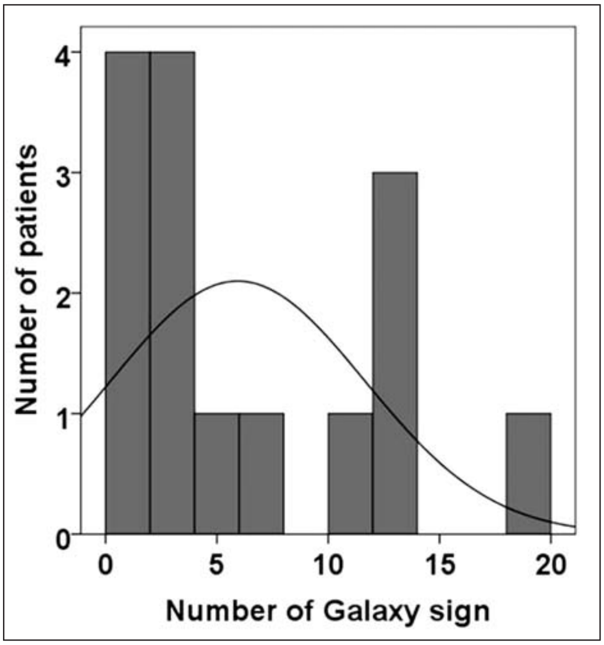

Fig. 3. Histogram of the galaxy sign number frequency in patients. There was a bimodal relationship between the galaxy sign frequency per patient (1-6, 11-15), with a mean number of 5.3 nodes per patient (median 3.0)

Table 2. Comparison of clinical data between galaxy sign-positive and negative groups

	Galaxy sign-negative group (n=50)	Galaxy sign-positive group (n=15)	p value
Serum (median, IQR)			
ACE (U/L)	25.3 (19.1-31.7)	24.1 (17.4-33.9)	N.S
soluble IL-2R (U/mL)	1050 (669-1715)	1080 (591-2552)	N.S
Ca	9.5 (9.3-9.7)	9.5 (9.3-9.6)	N.S
BALF (median, IQR)			
TCC (× 10^5)	1.3 (0.7-2.3)	1.8 (1.05-2.7)	N.S
Neutrophils (%)	1.0 (1.0-1.0)	1.0 (1.0-)	N.S
Lymphocytes (%)	28 (12.8-40.3)	13 (9.0-56)	N.S
Macrophages (%)	72 (60-85.5)	86 (43-90.5)	N.S
CD4/CD8	5.8 (3.7-8.6)	2.6 (2.0-3.9)	p=0.001
CD4/CD8 >3.5	26/33 (78.8%)	2/7 (28.6%)	p=0.017
Pulmonary function test	n=18	n=5	
VC, % predicted (mean±SD)	91.8±28.5	98.9±12.2	N.S
FEV1.0% (mean±SD)	81.4±5.8	85.9±3.7	N.S
DLco, % predicted (mean±SD)	97.1±11.9	86.0±20.8	N.S

Ca: calcium; ACE: angiotensin converting enzyme, BALF: bronchoalveolar lavage fluid,
soluble IL-2R: soluble interleukin-2 receptor, TCC: total cell count, NA: not available.
BALF was analyzed in 14 and 24 patients in galaxy sign-positive and negative groups, respectively.

Distribution of galaxy sign

Among the 89 total galaxy signs, nodules were statistically more frequent in the upper lung field (median 1.0, range 0-8) than the lower field (median 0, range 0-9) (p=0.009) (Fig. 4). Regarding horizontal analysis of the galaxy sign distribution, no significant difference was found in either the right or left lung between the upper, middle, and lower lung fields (Fig. 4).

Discussion

This study demonstrated the first evidence of diagnostic accuracy of the galaxy sign in the differentiation of pulmonary sarcoidosis from pulmonary tuberculosis with a high specificity (98%). No correlation was observed between galaxy signs and disease severity or degree of extrapulmonary involvement.

The galaxy sign pathologically corresponds to coalescent granulomas, and it was first reported by Nakatsu et al. (1) as a specific radiologic finding of pulmonary sarcoidosis, with a frequency of 27%. However, pulmonary sarcoidosis is well known for diverse radiological manifestations (3, 4), and the precise role of imaging in sarcoidosis diagnosis remains undefined (5).

Among our 65 patients with sarcoidosis, the median number of galaxy signs was 3.5 per patient,

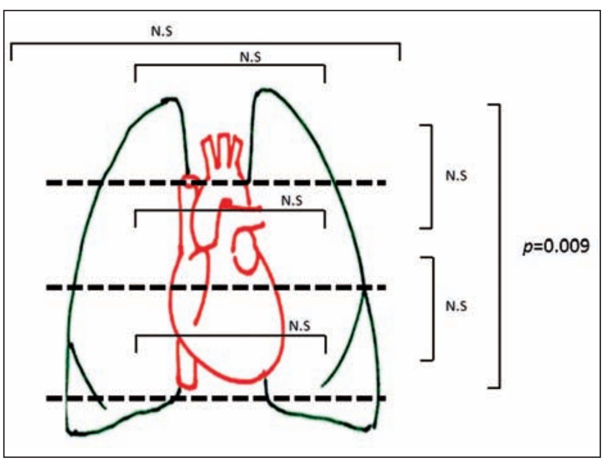

Fig. 4. Comparisons of the number of the galaxy signs in the upper, middle, and lower lung fields. There were significantly more nodes in the upper field (median 1.0, range 0-8) than the lower field (median 0, range 0-9) (p=0.009). Horizontal analysis of the galaxy sign distribution was similar in right and left hemithorax.

which were most commonly located in the upper lung field compared to the lower lung field, but signs were equally distributed between the right and left sides. No difference was found in galaxy sign size using horizontal or vertical analysis. Approximately 40% of patients had eye lesions in both the galaxy sign-positive and negative groups, which was similar to previously reported data (6). Of note, the present study newly demonstrated no between the galaxy signs and steroid use, advent of neurological or cardiac involvement, or number of organs involved. Sarcoidosis is a systemic disease (7-9), and specifically in Japan, 77% of deaths ascribed to sarcoidosis are due to cardiac involvement (10). In this regard, the fact would be useful for physicians.

We also found that the galaxy sign-positive group had significantly lower BALF CD4/CD8 ratios than of the galaxy sign negative group (p=0.001), which was maintained even if the threshold was defined as 3.5 (p=0.017) (Table 2). Furthermore, the proportion of smokers in both groups was similar, and no other factors for decreasing CD4/CD8 ratio were noted. Costabel et al. (11, 12) reported that a ratio ≥3.5 had a sensitivity of 52% and specificity of 94% in 117 consecutive patients with biopsy-proven sarcoidosis. However, in this study, only 28.6% of patients with galaxy signs had CD4/CD8 ratios greater than 3.5, whereas 78.8% of patients without galaxy signs had such ratios (Table 2). This result suggests that for patients suspected of having sarcoidosis with BALF CD4/CD8 ratios less than 3.5, galaxy signs would further suggest a diagnosis of pulmonary sarcoidosis. Agnostini et al (13). characterized the total number of 394 patients with pulmonary sarcoidosis who satisfied both CD4/CD8 ratio less than 1.0 and lymphocyte alveolitis. Among them, only 3.8% (n=15) patients had CD8 alveolitis probably due to reflect a homing of memory cells against for unknown antigen in the lung. However, we did not perform the immunohistochemical staining with CD4 or CD8 in individual cases. Therefore, we cannot precisely explain the relationship between Galaxy sign and BALF CD4/CD8 ratio.

Another aspect should be taken into consideration: the Galaxy sign positive group was significantly younger than Galaxy negative group. Tanimoto et al. (14) reported that the low CD4/CD8 ratio in the BALF (less than 1.0) group seemed to be younger (38.1±12.9 years) than that of high CD4/CD8 ratio (higher than 4.0) group (45.5±12.8 years), as was the present study. But those data are not statistically significant thereby underestimated various factors might affect the result of CD4/CD8 ratio.

This study has some limitations. First, it was conducted in a small, single-institution cohort and was retrospective. Secondly, scarce data were available for the comparison group (tuberculosis). Thirdly, we did not have enough follow-up data to investigate the predictive role of galaxy signs for disease outcomes.

We concluded that the galaxy sign could be a specific radiological tool to differentiate pulmonary sarcoidosis from tuberculosis. A large, prospective multi-center cohort study is needed to clarify the clinical significance of the galaxy sign in sarcoidosis.

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