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Age is an independent predictor in pathological diagnosis of sarcoidosis: a retrospective analysis of diagnosis by endobronchial ultrasound-guided transbronchial needle aspiration

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Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the current major modality for the diagnosis of sarcoidosis with hilar and mediastinal lymphadenopathy because of its higher diagnostic yield and safety; however, predictors for the pathological diagnosis of sarcoidosis by EBUS-TBNA remain uncertain. The objective of this study was to determine a novel predictor for the pathological diagnosis of sarcoidosis by EBUS-TBNA.

Methods: Patients with pathological and/or clinical diagnosis of sarcoidosis were identified from patients who underwent EBUS-TBNA between February 2010 and December 2017, retrospectively. We extracted data on age, sex, stage of disease, number of punctured lymph nodes, number of punctures per procedure and target lymph node, and size of punctured lymph node. Next, we divided patients into groups of pathological positive and negative by EBUS-TBNA, and multivariate logistic regression analysis was performed following univariate analyses to evaluate the efficacy of these parameters as a predictive factor of the pathological diagnosis of sarcoidosis by EBUS-TBNA.

Results: We selected 89 patients involving 115 mediastinal and hilar lymph nodes. The diagnostic yield of sarcoidosis by EBUS-TBNA was 74/89 (83.1%). There were no significant differences in the size of lymph node and number of punctures between the groups, there was a significant difference in age by univariate analyses. In addition, multivariate logistic regression revealed that age was significantly associated with pathological diagnosis of sarcoidosis by EBUS-TBNA [5 years = 1 unit, odds ratio (OR), 0.79; 95% CI, 0.64–0.97; P=0.03].

Conclusions: The diagnostic yield of sarcoidosis by EBUS-TBNA was higher in younger than older patients. Therefore, age may be a novel independent predictor for the pathological diagnosis of sarcoidosis by EBUS-TBNA.

Keywords: Sarcoidosis; endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); pathological diagnosis; predictor; age

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Introduction

Sarcoidosis is a multisystem disorder of unknown etiology. The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by pathological findings which is typically noncaseating epithelioid-cell granulomas in one or more organs (1,2). Previous epidemiological studies have reported that thoracic lesions, including hilar and mediastinal lymphadenopathy and/or pulmonary parenchymal lesions, are most frequently observed in patients with sarcoidosis (3,4). Thus, pathological evaluation of thoracic lesions is important for a definitive diagnosis.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a useful modality for the diagnosis of thoracic lymphadenopathy, including primary lung cancer, malignant lymphoma, and sarcoidosis (5). Before the development of EBUS-TBNA, transbronchial lung biopsy (TBLB) by conventional bronchoscopy was the common method for pathological diagnosis of sarcoidosis. However, a recent meta-analysis showed that the diagnostic yield of sarcoidosis by EBUS-TBNA was significantly higher than by conventional TBLB (6). Another review article also showed high sensitivity and safety of EBUS-TBNA for the pathological diagnosis of sarcoidosis. For example, the diagnostic yield of EBUS-TBNA for a patient with sarcoidosis with hilar or/and mediastinal lymphadenopathy ranged from 54% to 93%, and the diagnostic accuracy was 79% (95% CI, 71–86%) (7). Thus, EBUS-TBNA is the major modality for the diagnosis of thoracic sarcoidosis.

Few studies have evaluated the predictors for a pathological diagnosis of sarcoidosis by EBUS-TBNA. One retrospective study showed no association between the size of the lymph node and number of passes (8). Another prospective study demonstrated that the short-axis diameter of lymph node, stage of disease, and number of passes were independent predictive factors associated with positive pathological findings of sarcoidosis (9). Results from these previous reports suggest that investigating the predictors for pathological diagnosis of sarcoidosis by EBUS-TBNA remain insufficient. Therefore, the objective of this study was to further assess a novel predictor for the pathological diagnosis of sarcoidosis by EBUS-TBNA.

Methods

We conducted a single-center retrospective study in the Department of Respiratory Medicine, Juntendo University Hospital (Tokyo, Japan). The study protocol was approved by the independent ethics committee of the institutional review board in Juntendo University Hospital (No. 17-125).

Patients were selected who were pathologically and/or clinically diagnosed with sarcoidosis from 631 patients who had undergone EBUS-TBNA between February 2010 and December 2017. Sarcoidosis was diagnosed based on the criteria of "Diagnostic Standard and Guideline for Sarcoidosis 2015" established by the Japan Society of Sarcoidosis and other Granulomatous Disorders. Patient with a "pathological" or "clinical" diagnosis of sarcoidosis based on these criteria were enrolled in this study. Systemic evaluations for sarcoidosis to detect other organ's lesions involving ocular, heart and brain were performed in pathological positive group and clinically highly suspected group.

EBUS-TBNA was performed using a convex endobronchial ultrasound bronchoscope probe (BF-UC260FW; Olympus, Tokyo, Japan) under the sedation by pethidine (17.5 mg/body) and midazolam (2–4 mg/body) in all enrolled patients. A dedicated 22-gauge needle (NA-201SX-4022; Olympus, Tokyo, Japan) was used for the punctures. EBUS-TBNA was performed without rapid on-site evaluation of samples. All procedures were performed as previously described (10).

After evaluation of characteristics, patients and punctured lymph nodes were divided into groups of pathological positive and negative by EBUS-TBNA. We defined positive pathological findings as epithelioid granuloma without caseous necrosis. Univariate analyses of patients were performed on variables of age (5 years was regarded as 1 unit), gender, stage, total number of punctures per procedure, and the number of punctured lymph nodes. In addition, univariate analyses of punctured lymph nodes were performed on stage, short and long-axis diameter of the target lymph node, and total number of punctures per lymph node. We chose these parameters by referring to previous studies. We also included some parameters of basic characteristics. The short and long-axis diameters of the lymph node were measured using computerized tomography.

We used *t*-test to compare continuous variables and chi-square tests for categorical variables. Multivariate logistic regression analysis was subsequently performed for parameters that reached $P<0.10$ in the univariate analyses in our study and factors that have been associated with a pathological positive diagnosis of sarcoidosis by EBUS-

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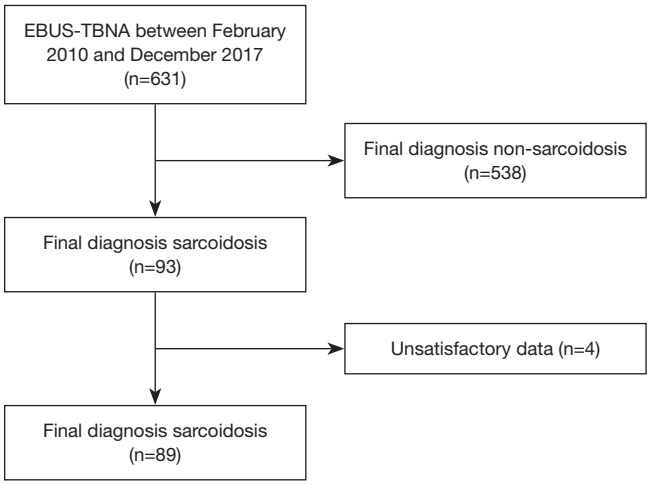

Figure 1 Flow diagram of patients with suspected sarcoidosis with hilar and/or mediastinal lymphadenopathy undergoing endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

TBNA in previous studies. These analyses were performed using Statistical Package for Social Science (SPSS) Version 19 software (Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results

We selected 93 patients finally diagnosed with sarcoidosis, and excluded four patients who did not have satisfactory data about evaluated parameters from 631 patients who had an EBUS-TBNA between February 2010 and December 2017 (*Figure 1*).

Characteristics of the 89 patients are shown in *Table 1*. Among the 89 patients (42 with stage I and 47 with stage II), 82 patients (92.1%) were pathologically diagnosed, and 74 of those patients (83.1% of the total) were diagnosed by EBUS-TBNA. Transbronchial lung, skin, cervical lymph node, and open lung biopsies were used for diagnosis in eight patients. A total of 115 mediastinal and hilar lymph nodes were punctured in these 89 patients. Characteristics of these lymph nodes are shown in *Table 2*. Stations of the punctured lymph nodes were #7 (67.8%), #4 (28.7%), and #11 (3.5%).

The mean short-axis and long-axis diameter was 15.5 and 14.7 mm, and 40.5 and 39.3 mm in the pathological positive and negative groups, respectively. There were no statistically significant differences in the size of the lymph node between groups. Statistical analysis also showed no significant differences in the number of punctures performed per each lymph node and stage of disease between the groups (*Table 3*).

While gender, stage, total number of passes during the

Table 1 Patient characteristics

Characteristics	Value (n=89)
Age, mean [range], years	51.8 [23–81]
Gender, N (%)	
Male	41 (46.1)
Female	48 (53.9)
Stage[a], N (%)	
I	42 (47.2)
II	47 (52.8)
Extra-pulmonary lesions, N (%)	
Yes	37 (41.6)
Eye	31 (34.8)
Skin	6 (6.7)
Central nerve	2 (2.2)
Heart	2 (2.2)
Cervical lymph node	2 (2.2)
No	52 (58.4)
Diagnosis, N (%)	
Pathological diagnosis method	82 (92.1)
EBUS-TBNA	74 (83.1)
TBLB	3 (3.4)
Skin biopsy	3 (3.4)
Cervical lymph node biopsy	1 (1.1)
Open lung biopsy	1 (1.1)
Clinical diagnosis	7 (7.9)
Number of total passes per patient, median [range]	2 [1–5]
Number of punctured lymph node stations, median [range]	1 [1–3]

[a], the stage of pulmonary sarcoidosis has been defined as follows. Stage I: only hilar and/or mediastinal lymphadenopathy; stage II: both thoracic lymphadenopathy and pulmonary parenchymal lesions. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

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procedure, and number of punctured lymph node stations were not significantly associated with pathological positive findings by EBUS-TBNA, age was significantly related to the positive findings of sarcoidosis by univariate analysis. Furthermore, multivariate logistic regression revealed that age was significantly associated with pathological positive findings by EBUS-TBNA [5 years was regarded as 1 unit, odds ratio (OR), 0.79; 95 % CI, 0.64–0.97; P=0.03] (*Table 4*). This result showed that the diagnostic yield of sarcoidosis by EBUS-TBNA was significantly higher in younger than older patients. Actual age of enrolled patients both in pathological positive and negative groups were shown in *Figure 2*.

Table 2 Characteristics of punctured lymph nodes

Characteristics	Value (n=115)
Station, n (%)	
#7	78 (67.8)
#4	33 (28.7)
#11	4 (3.5)
Mean of the short-axis diameter [range] (mm)	15.3 [5.9–28.3]
Mean of the long-axis diameter [range] (mm)	40.2 [10.9–93.4]
Median number of punctures per lymph node [range]	2 [1–5]

Discussion

In this study, we have assessed the predictive factors of positive pathological findings in sarcoidosis by EBUS-TBNA. First, we have shown that age was an independent predictor in the pathological diagnosis of sarcoidosis by EBUS-TBNA. Furthermore, age was significantly lower in pathological positive group than in negative group. Several parameters, which are associated with pathological positive findings by EBUS-TBNA in previous studies, were not predictors in this study.

Previously, a retrospective study has reported that

Table 3 Univariate analysis of clinical factors associated with pathological positive sarcoidosis diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal and hilar lymph nodes

Characteristic	Pathological positive cases (n=86)	Pathological negative cases (n=29)	Total (n=115)	Univariate P value
Stage (I/II)	44/42	13/16	57/58	0.56
Short-axis diameter (mm)	15.5	14.7	15.3	0.47
Long-axis diameter (mm)	40.5	39.3	40.2	0.73
Number of punctures per lymph node	2.02	1.93	2.00	0.62

Table 4 Univariate and multivariate analyses of clinical factors associated with pathological positive sarcoidosis diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration for patients

Characteristic	Pathological positive cases (n=74)	Pathological negative cases (n=15)	Total (n=89)	Univariate P value	Multivariate P value	Odds ratio	95% CI
Age, years	10.07[a] (50.32[b])	11.83[a] (59.13[b])	10.36[a] (51.8[b])	0.04	0.03	0.79[a]	0.64–0.97[a]
Gender (male/female)	34/40	7/8	41/48	0.96	–	–	–
Stage (I/II)	36/38	6/9	42/47	0.54	0.37	–	–
Total number of punctures per procedure	2.61	2.47	2.58	0.60	–	–	–
Number of punctured lymph node stations	1.32	1.13	1.29	0.09	0.15	–	–

[a], 5 years = 1 unit; [b], actual age.

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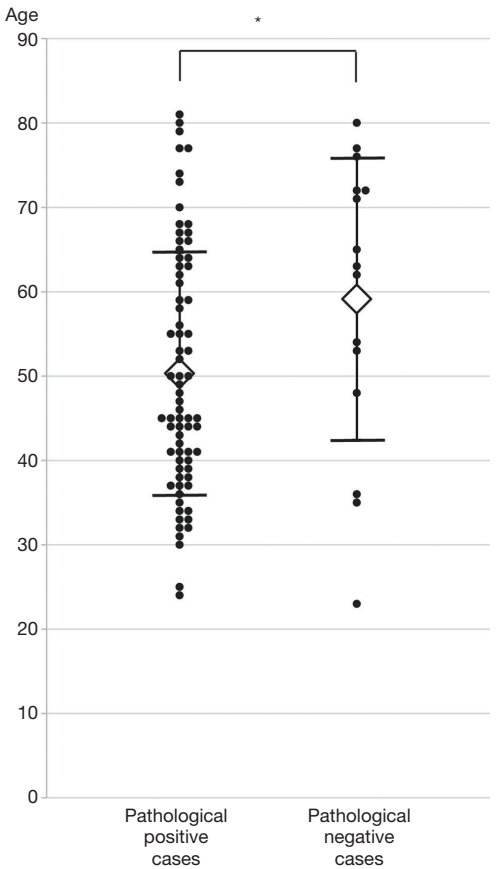

Figure 2 Individual ages of enrolled patients in pathological positive and negative groups. Plotted values are means ± SD. *, P<0.05.

needle gauge, size of lymph node, total number of needle passes, and number of lymph node stations sampled is not associated with the positive pathological findings of sarcoidosis by EBUS-TBNA; however, the skill of the operator was related to pathological diagnosis (8). In contrast, another prospective study has suggested that short axis, >1 pass per lymph node, and stage I diagnosis are independent predictive factors associated with diagnostic yield by EBUS-TBNA (9). Additionally, Oki *et al.* have recently reported that ≥4 passes per patient for either single or multiple lesions was recommended for successful pathological diagnosis in sarcoidosis by EBUS-TBNA (11). Similar to our study, these reports evaluated the predictive factors in pathological diagnosis by EBUS-TBNA; however, the results are not completely consistent and predictive factors remain uncertain. Moreover, these studies did not evaluate age as a predictor for successful pathological diagnosis of sarcoidosis by EBUS-TBNA.

This study showed that the age of pathological positive group by EBUS-TBNA was significantly lower than the negative group. This result may be explained using the biological and epidemiological backgrounds of sarcoidosis. The pathogenesis of sarcoidosis is a granulomatous immune reaction to environmental antigens, such as *Propionibacterium acnes* or *Mycobacterium species*, mainly caused by type 1 helper T cells (Th-1) (12). Antigen-presenting cells, including macrophages and dendritic cells, cause an exaggeration of Th-1 cell proliferation, which results in intra- and/or extra-thoracic granulomatous formations (13). Moreover, recent investigations suggested the modulatory function of regulatory T cells (Tregs) in the immune reaction of sarcoidosis. A previous study indicated that the number of Tregs in an elderly group was significantly increased when compared with a younger group in an animal model, and there was a direct correlation between the expansion of Tregs and immune deficiency in aged animals (14). A recent epidemiological study in Japan showed that the incidence of thoracic lymphadenopathy was higher in a patient group <45 years of age, suggesting a progressive decline in immune response with age (15). This may lead to lower diagnostic yield of sarcoidosis by EBUS-TBNA in older patients. Therefore, our results strongly recommend the use of EBUS-TBNA for younger patients in the diagnosis of sarcoidosis.

Conversely, a recent epidemiological study showed that age at diagnosis has gradually increased over the past four decades in Japan and western countries (3,4). Reduced exposure to microbial agents in early life, which could elevate the risk of developing sarcoidosis, may reflect the increasing age of disease onset in recent decades. Interestingly, the age at diagnosis of sarcoidosis in this study was relatively high compared with previous reports, even in the pathological positive group; therefore, the onset and age at diagnosis of sarcoidosis may increase in the near future.

Several limitations of this study should be mentioned. First, this study was a retrospective analysis with a small number of patients in single institution, which may account for the discrepancy in results between this and previous studies in the analysis of predictive factors. Second, we have speculated about differences in immune response that are dependent on age accounting for our results; however, we have not assessed immune reactivity of patients in this study, so this cannot be confirmed. Third, we have not verified all previously evaluated predictors. For example, a previous

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prospective study indicated that ≥4 passes can lead to a pathological positive (11), the mean number of passes in this study was less than that of the previous report. Moreover, we could not assess the skill of the operator on effective pathological diagnosis. Fourth, this study had assessed only Japanese patients. Frequency of sarcoidosis probably depends on each ethnicity. Further prospective investigation including variety of ethnicity is needed in the future.

In summary, we have investigated predictive factors for the pathological diagnosis of sarcoidosis by EBUS-TBNA. The diagnostic yield of sarcoidosis by EBUS-TBNA was higher in younger than older patient; therefore, age may be an independent predictor for the pathological diagnosis of sarcoidosis by EBUS-TBNA. We may have to select the modality in the diagnosis of sarcoidosis depending on patient's age.

Acknowledgments

None

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the independent ethics committee of the institutional review board in Juntendo University Hospital (No. 17-125).

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