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【 CASE REPORT 】

Pulmonary Nodular Lymphoid Hyperplasia Evaluated with Bronchoalveolar Lavage Fluid Findings: A Case Report and Review of the Literature on Japanese Patients

Sakiko Moriyama[1], Takashi Kido[1], Noriho Sakamoto[1], Mai Fuchigami[2], Takatomo Tokito[1], Daisuke Okuno[1], Takuto Miyamura[1], Shota Nakashima[1], Atsuko Hara[1], Hiroshi Ishimoto[1], Yoshitaka Imaizumi[3], Kazuto Tsuruda[2], Katsunori Yanagihara[2], Junya Fukuoka[4] and Hiroshi Mukae[1]

Abstract:

Pulmonary nodular lymphoid hyperplasia (PNLH) is a very rare disease, and it is difficult to diagnose PNLH and distinguish it from mucosa-associated lymphoid tissue (MALT) lymphoma. In addition, information on bronchoalveolar lavage fluid (BALF) analyses is lacking. We herein report a 36-year-old Japanese woman diagnosed with PLNH by a surgical biopsy and analysis of BALF. The BALF showed an increase in B-cell marker-positive lymphocytes, normal patterns of B-cell clonality, *mucosa-associated lymphoid tissue 1 gene*, and *immunoglobulin heavy chain* at 14q32 translocations. We also reviewed Japanese cases of PNLH described in Japanese or English to explore the characteristics of such cases.

Key words: bronchoalveolar lavage fluid, gene translocation, *immunoglobulin heavy chain*, mucosa-associated lymphoid tissue lymphoma, pulmonary nodular lymphoid hyperplasia

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Introduction

Pulmonary nodular lymphoid hyperplasia (PNLH) is a very rare disease characterized by nonclonal lymphoproliferation that usually forms a single nodule but rarely forms multiple pulmonary nodules (1). The typical histology is follicular hyperplasia, interfollicular plasmacytosis, and a variable degree of fibrosis. Findings of immunohistochemical analyses for markers, such as CD3 and CD20, are consistent with a reactive process and no aberrant lymphocyte phenotype (2).

PNLH features are also involved in mucosa-associated lymphoid tissue (MALT) lymphoma. However, in contrast to MALT lymphoma, none of the following features are present in PNLH: lymphoepithelial lesions, amyloid deposits, B-cell clonality, light-chain restriction, or MALT lymphoma-associated gene translocation (1). It is difficult to exclude MALT lymphoma from the diagnosis of PNLH without surgical excision. Thus, less-invasive methods and the accumulation of further evidence and clinical and laboratory findings of PNLH are awaited.

We herein report a Japanese patient with PNLH diagnosed using a surgical biopsy in addition to the assessment of CD markers, clonality, and MALT lymphoma-associated gene translocation in bronchoalveolar lavage fluid (BALF). We also reviewed 13 Japanese cases of PNLH described in Japanese or English to gather evidence and explored the characteristics of this rare disease.

[1]Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Japan, [2]Department of Laboratory Medicine, Nagasaki University Hospital, Japan, [3]Department of Hematology, Nagasaki University Hospital, Japan and [4]Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Japan
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Correspondence to Dr. Takashi Kido, t-kido@nagasaki-u.ac.jp

Table 1. Main Laboratory Results in Our Patient at 36 Years Old.

Hematology		LDH	169 U/L	Anti SM Ab	0.7 U/mL
WBC	4,400/μL	CRP	0.80 mg/dL	Anti RNP Ab	5.3 U/mL
Neut	82%			MPO-ANCA	<1.0 U/mL
Lymph	9%	Serology		PR3-ANCA	<1.0 U/mL
Mono	6%	KL-6	311 U/mL	Anti Scl-70 Ab	12.4 U/mL
Eosino	3%	SP-D	78.6 ng/mL	Anti ss-DNA Ab	4.6 AU/mL
Baso	0%	ACE	14.3 U/L	Anti ds-DNA Ab	1.9 IU/mL
RBC	409×10^4/μL	IL-6	3.29 pg/mL		
Hb	12.1 g/dL	sIL-2R	251 U/mL	Pulmonary function test	
PLT	15.8×10^4/μL	IgG	2,432 mg/dL	VC	3.11 L
		IgG4	108 mg/dL	%VC	108.3%
Biochemistry		IgG4/IgG	4.4%	FEV_1	2.77 L
Na	135 mmol/L	Antibody		FEV_1%	89.6%
K	3.4 mmol/L	ANA	<20	DL_{CO}	14.7 mL/min/mmHg
AST	22 U/L	Anti CCP Ab	<0.1 U/mL	$\%DL_{CO}$	74.9%
ALT	34 U/L	Anti SS-A Ab	0.7 U/mL		
BUN	8 mg/dL	Anti SS-B Ab	1.2 U/mL		
Cre	0.46 mg/dL	Anti CCP Ab	<0.1 U/mL		

Ab: antibody, Baso: basophils, Eosino: eosinophils, lymph: lymphocytes, Neut: neutrophils, mono: monocytes, Hb: hemoglobin, RBC: red blood cells, WBC: white blood cells, PLT: platelets, Na: sodium, K: potassium, ALT: alanine transaminase, AST: aspartate transaminase, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, LDH: lactate dehydrogenase, VC: vital capacity, FEV: forced expiratory volume, DL_{co}: carbon monoxide diffusion capacity, SM: Smith, RNP: ribonucleoprotein, ANCA: anti-neutrophilic cytoplasmic autoantibody, DNA: deoxyribose nucleic acid, IL: interleukin, sIL: soluble interleukin, ACE: angiotensin converting enzyme, ANA: antinuclear antibody, CPP: cyclic citrullinated peptide, SS: Sjögren's syndrome, Scl: scleroderma, Ig: immunoglobulin, SP-D: surfactant protein-D, KL-6: Krebs von den Lungen-6

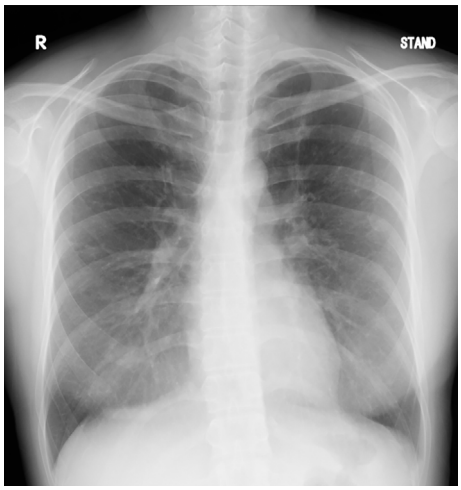

Figure 1. Chest radiograph. Chest radiograph showing multiple ground-glass opacities in the bilateral lung fields.

Case Report

A 36-year-old Japanese woman was referred to our hospital because of a persistent dry cough. She was a non-smoker and worked as an elementary school teacher. On admission, her body temperature, pulse rate, and respiratory rate were 36.5°C, 83 beats/min, and 16 breaths/min, respectively. Respiratory sounds were clear. Clubbed fingers were not observed.

The main laboratory results are shown in Table 1. The white blood cell count was within the normal range, and the C-reactive protein level was slightly elevated. No increase in interstitial pneumonia markers, such as Krebs von den Lungen-6 or surfactant protein-D, was noted. The angiotensin-converting enzyme, interleukin-6, and soluble interleukin-2 receptor levels were within the respective normal ranges. Serum immunoglobulin G (IgG) and IgG4 levels were elevated, but the proportion of IgG4 was not elevated. Representative tests for collagen disease-related autoantibodies were all negative. The pulmonary function test results were within the respective normal ranges. The carbon monoxide diffusion capacity of the lung was slightly reduced.

Chest radiography (Fig. 1) showed multiple ground-glass opacities (GGOs) in the bilateral lung fields. Chest high-resolution computed tomography (CT) revealed multiple GGOs, nodules, and cyst formation in the bilateral lung fields (Fig. 2A). Lymphadenopathy was not observed. Positron emission tomography (PET)-CT showed positive results for shadows with a maximum standard uptake value (SUV) of 3.52. BALF obtained from the upper lobe (right B^1a) yielded 3.0×10^5 cells/mL (76.0% macrophages, 20.7% lymphocytes, 1.5% neutrophils, and 1.8% eosinophils) with a low CD4/CD8 ratio of 0.4. Pathological specimens obtained by a transbronchial lung biopsy through the right B^1a, B^1b, and B^2a bronchi showed no specific findings. Lung tissues of the right upper and middle lobes were then obtained via video-assisted thoracic surgery.

A histopathological examination showed a nodular lesion

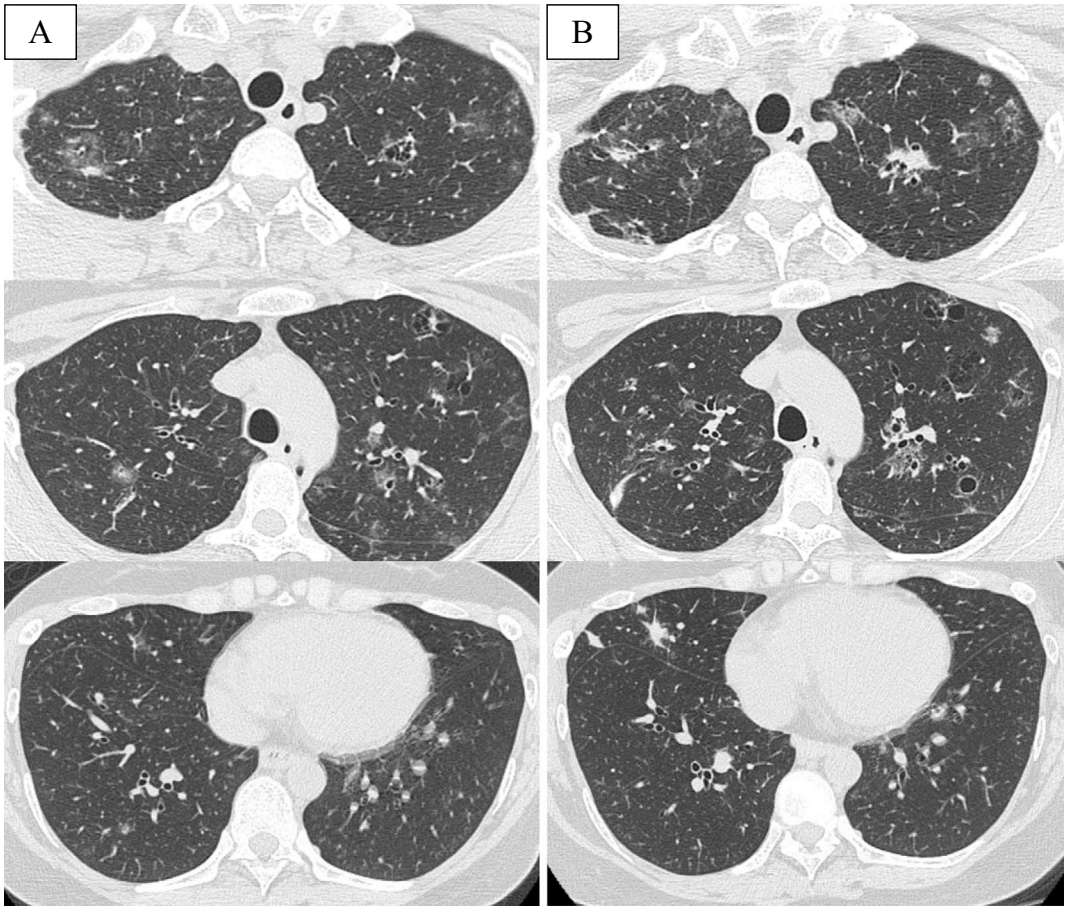

Figure 2. **Chest high-resolution computed tomography. Chest high-resolution computed tomography showing multiple ground-glass opacities, nodules, and cyst formation in the bilateral lung fields (A). Five years later, the findings had gradually worsened (B).**

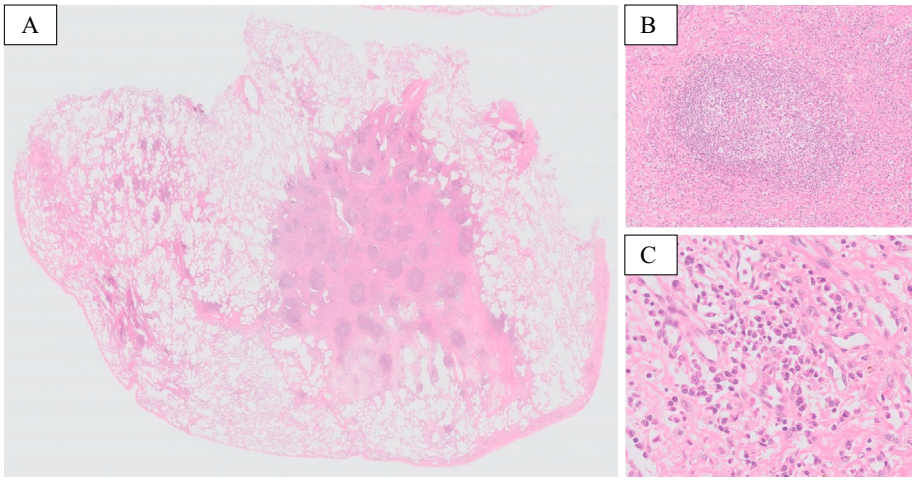

Figure 3. **Pathological findings from the lung specimens. Low- (A) and high- (B, C) magnification photomicrographs of pathological specimens obtained during video-assisted thoracic surgery. Nodular lesions with fibrosis (A), lymphoid follicles with numerous germinal centers (B), and infiltration of plasma cells (C) were observed. Lymphoepithelial lesions were not observed.**

with fibrosis, lymphoid follicles with numerous germinal centers, and infiltration of plasma cells (Fig. 3). Immunostaining was positive for both T- and B-cell markers, such as CD3, CD20, and CD79a, indicating a polyclonal lymphoproliferative morphology. Immunohistochemically, the IgG4/IgG ratio was high (>70%). Lymphoepithelial lesions, amyloid deposits, eosinophil infiltration, and vasculitis were not observed. An additional examination for the *immu-*

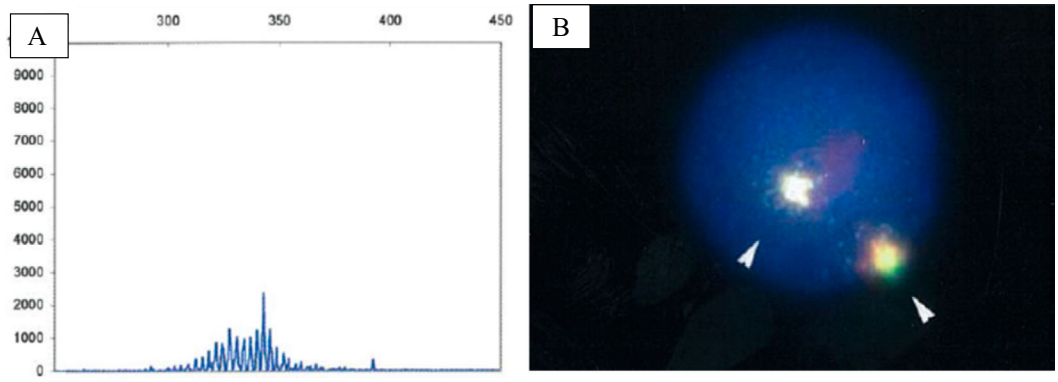

Figure 4. Analyses of the bronchoalveolar lavage fluid (BALF) with molecular biology techniques. (A) Negative results (nonclonal peaks) in the VH (FR1)/JH region for *immunoglobulin heavy chain* gene rearrangement for the evaluation of B-cell clonality using polymerase chain reaction (PCR). (B) Fusion signals of *mucosa-associated lymphoid tissue 1* evaluated by fluorescence *in situ* hybridization with lymphocytes in BALF, suggesting no translocation of the specific gene of mucosa-associated lymphoid tissue lymphoma.

noglobulin heavy chain (*IgH*) gene rearrangements for the evaluation of B-cell clonality was recommended by pathologists to confirm the diagnosis. However, it could not be performed because of the lack and condition of the lung tissues. Thus, we suspected PNLH, but could not completely exclude lymphoma at that time.

Corticosteroid therapy [prednisolone (0.5 mg/kg/day)] was initiated with the expectation of a favorable effect on any present lymphoproliferative disease, such as IgG4-related disease. The dry cough symptom partially improved; however, the radiological findings did not improve, and prednisolone was gradually decreased and stopped within seven months. Five years later, a re-evaluation of the BALF for diffuse lung disease from the right B[5] was performed because the radiological findings had gradually worsened with no remarkable change in her symptoms or lung function (Fig. 2B). The results showed 3.5×10^5 cells/mL with an increase in lymphocytes (27.0% lymphocytes), and CD3-, CD 4-, CD8-, CD19-, CD20-, sIgκ- and sIgλ-positive lymphocyte levels were 74.2%, 44.5%, 32.0%, 9.6%, 9.2%, 5.9%, and 4.1%, respectively, while the sIgκ/sIgλ ratio was 1.44. Polymerase chain reaction analyses of the VH (FR1)/JH, VH (FR2)/JH, VH (FR3)/JH, DH1-6/JH, and DH7/JH regions for *IgH* gene rearrangements for the evaluation of B-cell clonality and analysis for translocations of the *mucosa-associated lymphoid tissue 1 gene* (*MALT1*) at 18q21 and *IgH* at 14q32 in BALF via fluorescence *in situ* hybridization showed normal patterns (Fig. 4). Accordingly, we finally diagnosed the patient with PNLH based on the findings of nonclonal lymphoproliferation forming multiple pulmonary nodules with follicular hyperplasia, interfollicular plasmacytosis, and absence of lymphoepithelial lesions, amyloid deposits, or gene translocations, which suggest MALT lymphoma.

The detection of *IgH* rearrangements and *MALT1* and *IgH* translocations in BALF was approved by Nagasaki University Hospital Clinical Research Ethics Committee (Approval number: 19111804), with written informed content obtained from the patient.

Discussion

We herein report a case of PNLH that was suspected based on the findings of a surgical lung biopsy, but we were unable to exclude lymphoma without assessing clonality because of the lack of and condition of the lung tissues. The radiological findings had gradually worsened over a period of five years following the initial presentation, despite corticosteroid therapy. Thus, we re-evaluated the BALF and found an increase in the proportion of lymphocytes, and neither *IgH* rearrangement nor *MALT1* and *IgH* translocation associated with MALT lymphoma were observed. Therefore, we confirmed the diagnosis of PNLH.

The BALF findings of PNLH have not been well-described. In the present case, an increase in lymphocytes (27.0% lymphocytes) and a slight increase in the number of B-cell markers (CD19 and CD20, 9.6% and 9.2%, respectively) were observed. Lymphocytic alveolitis is indicative of the possibility of pulmonary lymphomas, especially with an increase in the B-cells of more than approximately 10% (3). We confirmed negative findings for *IgH* rearrangement in addition to an sIgκ/sIgλ ratio in the normal range (1.44) for the evaluation of B-cell clonality and *MALT1* and *IgH* translocations in BALF. The sensitivity and specificity of *IgH* rearrangements using BALF for B-cell pulmonary lymphomas are both approximately 90% (4-6). *MALT1* and *IgH* translocations have been frequently detected in MALT lymphomas and can also be detected in BALF (7-9). The present case and previous reports suggest that biological analyses, including the confirmation of negative results of clonality and gene rearrangements, might be useful as less-invasive techniques for diagnosing PNLH.

To accumulate clinical and laboratory findings of PNLH, which is a very rare disease, we reviewed Japanese cases of

Table 2. Clinical Characteristics of Japanese Patients with Pulmonary Nodular Lymphoid Hyperplasia.

No	Reference	Year	Age	Sex	Symptom	Underlying disease	Smoking history	CRP	sIL-2R	CT findings	Solitary or Multiple	Distribution in the lungs	SUV in PET-CT
1	14	1996	73	M	Cough and hemoptysis	Cerebral infarction and abdominal aortic aneurysm	NA	NA	NA	Mass	Solitary	Right upper lobe	NA
2	12	2005	49	F	General fatigue	NA	NA	NA	NA	Nodule and GGO	Multiple	Diffuse	NA
3	18	2007	67	F	None	Multiple sclerosis	NA	NA	NA	Nodule	Solitary	Right lower lobe	NA
4	17	2009	68	F	Cough	NA	NA	NA	NA	Nodule and GGO	Multiple	Right middle and lower lobes	6.05
5	15	2009	71	F	None	Sjogren's syndrome	NA	NA	NA	GGO	Solitary	Right lower lobes	NA
6	19	2009	67	M	Cough and exertional dyspnea	Synovial sarcoma	NA	NA	659	Nodule	Multiple	Diffuse	1.4-2.7
7	13	2009	18	F	None	NA	NA	NA	NA	GGO	Solitary	Left lower lobe	2.4
8	16	2010	50	M	None	Hypertension, hyperlipidemia, and asthma	NA	NA	NA	Nodule and cyst	Multiple	Diffuse	NA
9	11	2013	70	M	None	Hypertension	50 pack-years	NA	NA	Mass	Solitary	Right middle to lower lobes	4
10	10	2019	56	F	Hemoptysis	Collagen disease	Never	0.91	628	Nodule and GGO	Multiple	Diffuse	NA
11	21	2020	86	M	Cough and hemoptysis	NA	38 pack-years	NA	NA	Mass	Solitary	Right middle lobes	7.8
12	20	2020	61	M	None	NA	40 pack-years	NA	NA	Nodule	Solitary	Right lower lobes	Negative
13	Present case	2020	36	F	Cough	None	Never	0.8	251	Nodule, GGO, and cyst	Multiple	Diffuse	3.52

CRP: C-reactive protein, CT: computed tomography, GGO: ground-glass opacity, NA: not available, sIL-2R: soluble interleukin-2 receptor, SUV: standard uptake value, PET: positron emission tomography

PNLH described in Japanese or English. Thirteen cases of PNLH, including the present case, have been reported in Japan (Table 2-4) (10-21). In summary, the median age of the patients was 67 (range: 18-86) years old, and there were 6 men (46.2%) and 7 women. Six patients (46.2%) were asymptomatic, 5 (38.5%) had a cough, and 3 had hemoptysis (23.1%). Three patients (23.1%) had a smoking history. These findings are similar to those of previous reports. It has been shown that most patients were middle-aged and older adults, and no sex-based differences were found (1, 22, 23). In the largest study of PNLH, which included 67 patients and was conducted by Fang et al. in 2019 from China, 35 patients (52.2%) were men, and their median age was 57 (range: 25-72) years old. It has also been reported that approximately half of the patients (36 patients, 53.7%) had no symptoms, such as cough (26 patients, 38.8%) or hemoptysis (16 patients, 21.9%), and 21 patients (31.3%) had a history of smoking (22). In a study involving Japanese patients, one patient had Sjogren's syndrome (15). Sjogren's syndrome was also observed in 1 of 67 patients (1.5%), and PNLH has the potential to share characteristics with autoimmune diseases, such as Sjogren's syndrome. However, the evidence available was inadequate to prove the correlation between the features of PLNH and Sjogren's syndrome (22-26).

Regarding the chest CT results of 13 Japanese patients with PNLH, 8 (61.5%) showed nodules, 6 (46.2%) showed GGO, 3 (23.1%) showed a mass, and 2 (15.4%) showed cysts. Seven patients (53.8%) had solitary lesions, and 6 (46.2%) showed multiple lesions. Solitary lesions were more likely to be located in the lower (5 out of 7, 71.4%) than upper and milddle lobes. Seven patients were also examined using PET-CT; 6 were considered positive (range of SUV max: 2.4-7.8), and 1 was negative. Among 67 patients from China, 51 (81.0%) showed nodules, 46 (68.7%) had solitary lesions, and 21 (31.3%) had more than 2 lesions (22). Nodules of 62.8% of patients were observed in the lower lobes. PNLH can also present as cavitating nodules (27). In the 67 patients from China, 2 of the 3 patients who underwent PET-CT showed a slightly increased ^{18}F-fluorodeoxyglucose (FDG) uptake, with SUVs of 0.99 and 0.91, and another patient showed no FDG uptake (22). Our patient had a persistent dry cough, and chest CT showed multiple GGOs, nodules, and cyst formation in the bilateral lung fields, while

Table 3. BALF Findings, Diagnostic Procedure, Treatment, and Clinical Course of Japanese Patients with PNLH.

No	Lymphocytes in BALF (%)	Diagnostic procedure	IgG4/IgG cells in the lung tissue	Treatment	Observation period (after the surgical biopsy)	Clinical course (after the surgical biopsy)
1	NA	Surgical biopsy	NA	Surgical resection	NA	NA
2	NA	Surgical biopsy	NA	Partial resection and observation	3 months	Disappeared and shrunk
3	NA	Surgical biopsy	NA	Surgical resection	3 years	No relapse
4	NA	Surgical biopsy	NA	Partial resection and observation	NA	NA
5	14	Surgical biopsy	NA	Surgical resection	NA	NA
6	NA	Surgical biopsy	NA	Partial resection and observation	1 year	Disappeared and shrunk
7	NA	Surgical biopsy	NA	Surgical resection	2 years	No relapse
8	NA	Surgical biopsy	NA	Partial resection and observation	6 years	Disappeared and shrunk
9	NA	Surgical biopsy	NA	Surgical resection	NA	NA
10	NA	Surgical biopsy	20-30%	Partial resection and observation	6 months	No change
11	NA	Surgical biopsy	NA	Surgical resection	NA	No relapse
12	NA	Surgical biopsy	Small amount	Surgical resection	NA	NA
13	20.7	Surgical biopsy and BALF	>70%	Partial resection, prednisolone, and observation	5 years	Worsened

BALF: bronchoalveolar lavage fluid, PNLH: pulmonary nodular lymphoid hyperplasia, IgG: immunoglobulin G, NA: not available

Table 4. Summary of Japanese Patients with Pulmonary Nodular Lymphoid Hyperplasia.

Number of patients	13
Age, y (median)	18-86 (67)
Male, n (%)	6 (46.2)
Symptom, n (%)	
None	6 (46.2)
Cough	5 (38.5)
Hemoptysis	3 (23.1)
Others	2 (15.4)
Chest CT findings, n (%)	
Nodule	8 (61.5)
GGO	6 (46.2)
Mass	3 (23.1)
Cyst	2 (15.4)
Solitary	7 (53.8)
Multiple	6 (46.2)
Surgical biopsy, n (%)	13 (100)
Course (after the surgical biopsy), n (%)	
No relapse	4 (50.0)
Disappeared or shrunk	3 (37.5)
Worsened	1 (12.5)

CT: computed tomography, GGO: ground-glass opacity

PET-CT showed a slightly increased FDG uptake, which is consistent with a diagnosis of PNLH.

Unfortunately, these clinical and radiological examinations are non-specific, and blood tests are also unhelpful for the diagnosis (1, 22). Thus, it is extremely difficult to diagnose PNLH and differentiate it from malignant tumors, such as lung cancers or malignant lymphomas. Previously, a preoperative differential diagnosis of lung cancer was considered for 7 out of 13 patients, 15 out of 67 patients, and 7 out of 9 patients from Japan, China, and South Korea, respectively (11, 13, 14, 18, 19, 20-23). Ultimately, all 13 Japanese patients underwent a surgical biopsy for the diagnosis. In previous cases, patients were also diagnosed using surgical biopsies, including 67 cases from China and 9 cases from South Korea (22, 23).

Notably, 8 of the 13 Japanese cases studies which were describe the clinical course after the diagnosis in our review, four patients showed solitary shadows on chest CT, and another four patients showed multiple shadows on chest CT. Recurrence was not observed in any of the four patients with solitary shadows after surgical resection. Multiple shadows in 3 of the 4 patients (75.0%) regressed spontaneously. In contrast, the radiological findings of the patient in the present case gradually progressed. In general, the prognosis of PNLH is favorable. It has been shown that, in 50 patients with a median follow-up time of 43 months, all patients were alive, except for 1 who died accidentally after lobectomy, and there were no recurrent cases (22). Neither recurrence nor new lesions were observed during a follow-up period of 3-18 months in 9 patients (23). Furthermore, a surgical biopsy was performed for a 33-year-old woman with multiple shadows in Korea, where some remaining lesions regressed, while others progressed over 9 months, as per her chest CT findings (28). A standard treatment for PNLH has not been established, other than surgical resection for solitary nodules. There is no description of pharmacotherapy for Japanese patients other than the present case. In Ireland, a 26-year-old woman was treated with corticosteroid therapy, after which her symptoms improved, and multiple nodules remained stable or decreased in size (27). Corticosteroid

therapy was initiated in the present patient, and the symptoms of dry cough partially improved; however, the radiological findings showed no improvement. These two cases suggest that the anti-inflammatory action of corticosteroid therapy may be partially effective on PNLH. The prognosis of PNLH is generally favorable, and a cure is expected using a surgical biopsy for solitary diseases. For multiple diseases, appropriate pharmacotherapy has not been established, but spontaneous improvement or stable disease can be expected. The use of corticosteroids might relieve some symptoms, such as cough, but corticosteroids have side effects, so additional evidence for their efficacy is desired.

In the present case, the IgG4/IgG ratio in the lung tissue was high (>70%); however, the serum IgG4/IgG ratio was not elevated (4.4%). These results did not fulfill the criteria for IgG4-related disease, and resistance to corticosteroid treatment also suggested that it was not an IgG4-related disease. Notably, 3 out of 13 Japanese case studies in our review mentioned the IgG4/IgG ratio in the lung tissue, and only in the present case did the patient show a ratio of more than 40%, which is one of the criteria for diagnosing IgG4-related diseases (29). Two cases of PNLH with a high IgG4/IgG ratio in the lung tissue have been reported in two patients in Ireland, one of whom was followed up without any treatment. The second patient, who was treated with corticosteroids, is described earlier in the discussion (27). Furthermore, 3 out of 26 patients (11.5%) with PNLH showed an increase in the IgG4/IgG ratio of 0.43 (range, 0.41-0.46). One of the three patients was evaluated for serum IgG level but showed no elevation (30). In addition, it has been shown that the mean IgG4/IgG ratio of 0.35 in the lung tissues of six patients with PNLH was significantly higher than that of other lung diseases (31). Our present case and these previous reports suggest that the IgG4/IgG ratio in the lung may be high in patients with PNLH. The presence of eosinophils and vasculitis is suggestive of an IgG4-related disease rather than PNLH (32). We reconfirmed this in the present case, and there were no findings of eosinophil infiltration or vasculitis, supporting our diagnosis of PLNH.

In conclusion, we reported a Japanese patient with PNLH who was diagnosed based on a surgical biopsy in addition to the negative results of clonality and MALT lymphoma-associated gene translocation in BALF, with an increase in the proportion of lymphocytes noted. Based on the reports of 13 Japanese patients with PNLH, we concluded that the clinical and laboratory findings of such cases are non-specific, and all patients were diagnosed using a surgical biopsy, in addition to previous reports of 67 cases from China and 9 from Korea. Because PNLH is usually indolent, establishing a less-invasive diagnostic method is desired, and the accumulation of additional evidence from BALF analyses is also expected.

The authors state that they have no Conflict of Interest (COI).

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