ATS/JRS/ALAT Guidelines for Humidifier Lung and Summer-Type Hypersensitivity Pneumonitis

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Abstract

Background: The ATS/JRS/ALAT Guidelines for the Diagnosis of Hypersensitivity Pneumonitis (GL for HP) were published in 2020. Humidifier lung and summer-type HP are forms of HP, but it is unclear whether they can be diagnosed using the GL for HP. This study examined the level of confidence with which humidifier lung and summer-type HP can be diagnosed with the GL for HP.

Methods: Data from 23 patients with humidifier lung and 20 patients with summer-type HP (mean age, 67.3 and 57.4 years, respectively) diagnosed between October 2012 and January 2022 were retrospectively reviewed. We evaluated high resolution computed tomography (HRCT) patterns, bronchoalveolar lavage fluid (BALF) findings, exposures, and histopathological findings to determine the level of confidence with which a diagnosis of HP could be made using the GL for HP.

Results: HRCT pattern was classified as typical HP in 5 (22%) and compatible with HP in 18 (78%) patients with humidifier lung and judged as typical HP in 17 (85%) and compatible with HP in 3 (15%) summer-type-HP patients. The confidence level for diagnosis of HP was definite in 2 (8.7%), moderate in 14 (60.9%), and low in 7 (30.4%) patients with humidifier lung. It was definite in 12 (60%), high in 3 (15%), and moderate in 5 (25%) patients with summer-type HP.

Conclusions: The GL for HP showed utility in the diagnosis of humidifier lung in many patients with a moderate to low confidence. There was, however, a definite to high confidence for patients with summer-type HP.

1. Background

Hypersensitivity pneumonitis (HP) is an inflammatory lung disorder caused by sustained or repeated inhalation of various antigens. Identification of irritating antigens is requisite for diagnosis of HP, and thus provocation tests are useful. For some patients, symptoms improve by avoiding antigen exposure, but others may require corticosteroid treatment [1–3]. The ATS/JRS/ALAT Guidelines for the Diagnosis of Hypersensitivity Pneumonitis (GL for HP) were published in 2020 [1]. While the incidence of HP is reported to range from 0.3–0.9 per 100,000 globally, claims-based analysis reports an incidence of 1.67 to 2.71 per 100,000 in the US population [1]. There are several phenotypes HP, and these are classified based on the causative antigen as summer-type HP, humidifier lung, bird breeders' lung, hot-tub lung, and farmers' lung [1–3]. Most cases of summer-type HP and humidifier lung are classified as acute non-fibrotic HP. The humid weather and traditional wooden houses in Japan are thought to increase exposure to *Trichosporon asahii (T. asahii)* a rare fungal pathogen common in immunocompromised patients. The incidence of summer-type HP in Japan was reported to be high—greater than 70%—and its characteristic features are thus well understood [4, 5].

In contrast, another study describes a low incidence of humidifier lung in Japan —less than 5%—and its characteristic features are thus poorly understood [4, 5]. Ultrasonic humidifiers are frequently used to prevent dry indoor environments during winter in the areas on the Pacific side of Japan. Humidifier lung is

a phenotype of home environment HP. Humidifier use has been recommended for combating the spread of COVID-19 and so the frequency of humidifier lung is increasing. Contaminated ultrasonic humidifiers directly disperse causative antigens in 0.5-μm to 3-μm droplets that easily reach the distal airway. When ultrasonic humidifiers are not carefully cleaned the water is easily contaminated with microorganisms such as bacteria and fungi, including bacterial endotoxins [6–14]. In general, prolonged exposure to a contaminating fungal or bacterial antigen and/or endotoxin results in immune sensitization and causes immune-mediated lung injury in susceptible individuals [6–14].

The criteria for diagnosing this rare condition have not been standardized, however, the ATS/JRS/ALAT Guidelines for the Diagnosis of Hypersensitivity Pneumonitis (GL for HP) were published in 2020 [1] followed by the CHEST Guidelines for the Diagnosis and Evaluation of Hypersensitivity Pneumonitis [2] in 2021. We previously reported on the clinical, laboratory, and chest CT features that distinguish humidifier lung from summer-type HP [15]. Another study also described differences between humidifier lung and summer-type HP [16]. Therefore, we hypothesize that it is difficult to diagnose and differentiate humidifier lung from summer-type HP by using the GL for HP. Few studies have comprehensively evaluated whether humidifier lung and summer-type HP can be diagnosed with these guidelines. Therefore, this study sought to examine the level of diagnostic confidence for humidifier lung using the GL for HP compared with summer-type HP.

2. Methods

2.1 Study Subjects

We retrospectively reviewed data from 23 patients with humidifier lung (mean age, 67.3 years) and 20 patients with summer-type HP (mean age, 57.4 years) diagnosed between October 2012 through January 2022. High resolution computed tomography (HRCT) patterns, bronchoalveolar lavage fluid (BALF) findings, exposures, and histopathological findings were also reviewed to determine the level of confidence with which the diagnosis of HP could be made based on the GL for HP. All confidence levels were classified by multidisciplinary discussion. Information from clinical records and physical examinations was analyzed, as were results from laboratory analyses, including serum white blood cell count (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), surfactant protein A (SP-A), and surfactant protein D (SP-D) levels, and arterial blood gas analysis.

2.2 Initial diagnosis of humidifier lung and summer-type HP

Humidifier lung was diagnosed from clinical and radiological findings by using a previously reported method [15] and the following criteria: 1) sustained presence of respiratory symptoms (such as cough, sputum, and dyspnea) for longer than 1 week; 2) bilateral ground-glass opacity (GGO) or consolidation on chest CT; 3) history of home ultrasonic humidifier use; 4) a positive provocation test result; 5) bronchoalveolar lavage findings or histopathological findings consistent with HP; and 6) improved symptoms, laboratory findings, and chest HRCT images after cessation of home ultrasonic humidifier use. Humidifier lung was diagnosed based on the presence of criteria 1, 2, 3, 4, and 5; criteria 1, 2, 3, 5,

and 6; criteria 1, 2, 3, and 4; or criteria 1, 2, 3, and 6 (probable). When diagnosed by using these criteria, the antigen exposure section of the GL for HP is judged “positive”. Summer-type HP was diagnosed based on typical clinical and chest HRCT findings as previously described [4, 5], and the presence of precipitating antibodies to *T. asahii*. Next, we evaluated the level of confidence of diagnosing non-fibrotic HP using the GL for HP.

2.3 Chest CT

Chest HRCT was performed on admission and during follow-up with a SOMATOM Definition AS, Flash and Edge scanner (Siemens Co., Ltd., Munich, Germany). The entire lung was scanned in 5-mm–thick sections. Additional thin-section CT (thickness, 1.0 mm) was performed for all patients to evaluate for parenchymal abnormalities. Thin-section CT images were reconstructed with a fixed window setting. Images were then independently reviewed by one thoracic radiologist (A.K.) and 3 pulmonologists (H.S., M.M., S.S.), all blinded to the identity and clinical, physiological, and pathological characteristics of the patients. Additionally, we determined which of the HRCT pattern criteria (nonfibrotic HP pattern) in the GL for HP were met. HRCT pattern was classified as typical and compatible with HP accordingly.

2.4 Bronchoalveolar lavage (BAL) and bronchoscopy

BAL was performed by using a standard method. BAL fluid (BALF) was purified by density-gradient centrifugation with BD vacutainer mononuclear cell preparation tubes and sodium heparin (Becton Dickinson and Company, Franklin Lakes, NJ). A differential count of the BALF cells was performed on cytocentrifuged smears stained with Wright-Giemsa. Flow cytometric analysis was used to determine the phenotype of T cells recovered from BALF. Transbronchial biopsy (TBLB) was performed after BAL, and 3 to 5 specimens were obtained within 1 week of hospital admission. TBLB specimens were evaluated for alveolitis, organization, bronchiolitis, eosinophilia, granuloma, alveolar epithelial cell hyperplasia, and giant cells. Pathological diagnosis was classified as typical, probable, or indeterminate according to the GL for HP (nonfibrotic HP).

2.5 Statistical analysis

Continuous variables are expressed as median (range), unless otherwise stated, and were compared by using the Mann–Whitney U test. Categorical variables were compared by using the χ^2 test. A P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed by using SPSS version 11.0 (SPSS Inc., Chicago, IL).

2.6 Ethical approval

This retrospective study was approved by the Institutional Review Board of Toho University Omori Medical Center in April 2022 (project approval number M20221). Considering the nature of the retrospective study, the informed consent was waived by the IRB because of the anonymized patient data. The study protocol was performed in accordance with the relevant guidelines.

3. Results

3.1 Patient characteristics

The characteristics of the 23 patients (17 men and 6 women) with humidifier lung and 20 patients (9 men and 11 women) with summer-type HP are shown in Table 1. Patients with humidifier lung were significantly older than those with summer-type HP (68.0±14.4 vs 57.4±17.6 years, respectively). Most patients with humidifier lung first visited the hospital in winter. Subacute to acute disease, with dyspnea, cough, and fever, was most common; the incidences of these symptoms did not differ significantly between patients with humidifier lung and summer-type HP (78.2% vs 85.0%, 87.0% vs 75.0%, and 73.9% vs 40.0%, respectively).

3.2 Laboratory findings

Table 2 shows the laboratory findings for both patient groups. Total WBC count as well as serum CRP and LDH levels were elevated in most patients. Both WBC count and CRP level were higher in humidifier lung than in summer-type HP (WBC: 13500±6500 vs 7500±2300/μL, P=0.003; CRP: 8.0±6.5 vs 2.1±2.7 mg/dL, P=0.004). Analysis of differential WBC cell counts showed a lower lymphocyte fraction for humidifier lung than for summer-type HP (13.2±7.2% vs 22.0±13.1%, P=0.008). Neutrophil fraction was higher in humidifier lung than in summer-type HP (79.4±9.5% vs 68.0±13.7%, P=0.003). Serum levels of KL-6 and SP-D were significantly lower in patients with humidifier lung than in those with summer-type HP (KL-6: 593.4±396.7 vs 2107.7±2029.7 U/mL, P=0.001; SP-D: 162.4±156.7 vs 579.8±505.8 ng/mL, P=0.001).

3.3 HRCT findings

Chest HRCT findings are shown in Table 3. The most common HRCT findings for humidifier lung and summer-type HP were faint GGO (95.6% vs 95.0%) and mosaic attenuation (52.2% vs 75.0%) (Fig. 1-A). Poorly-defined centrilobular micronodules were less common in humidifier lung than in summer-type HP (Fig. 2) (30.4% vs 65.0%, P=0.026). Diffuse non-segmental consolidation was seen bilaterally in 12 patients with humidifier lung; this is unusual in summer-type HP. This consolidation was more common in humidifier lung than in summer-type HP (52.1% vs 5.0%, P=0.002) (Fig. 1-B). HRCT pattern according to the GL for HP was typical HP in 5 (22%) and compatible with HP in 18 (78%) patients with humidifier lung and was typical HP in 17 (85%) and compatible with HP in 3 (15%) patients with summer-type HP (Fig. 3).

3.4 BALF

BAL was performed in 15 patients with humidifier lung and in all 19 patients with summer-type HP. BALF findings are shown in Table 4. Total BALF cell count was high in all patients with humidifier lung and those with summer-type HP. No significant difference was seen in total cell count, however, differential BALF cell count revealed lower increase in lymphocytes in humidifier lung than in summer-type HP (37.3±20.1% vs 69.0±22.6%, P<0.001). The percentage of patients with BALF lymphocyte count ratio greater than 20% was 15/19 (78.9%) in humidifier lung and 19/19 (100%) in summer-type HP. Neutrophil

fraction was greater in humidifier lung than in summer-type HP (22.1±25.6% vs 8.1±13.6%, P=0.157). Furthermore, the phenotypes of BAL lymphocytes differed significantly. BAL lymphocytes in humidifier lung were predominantly CD4+ lymphocytes, whereas those in summer-type HP were predominantly CD8+ lymphocytes. Thus, the CD4/CD8 ratio was significantly higher for humidifier lung than for summer-type HP (1.7±1.2 vs 0.8±0.9, P=0.003).

3.5 Pathological findings

Among the 15 patients with humidifier lung who underwent bronchoscopy, TBLB was performed in 9 because of worsening respiratory failure after BAL. Pathological findings of both groups are shown in Table 5. TBLB specimens from 9 patients with humidifier lung revealed alveolar septal wall thickening with lymphocyte infiltration (alveolitis) in all patients. Intra-alveolar organization was observed in 4 of the 9 patients with granulomatous inflammation and in 2 patients with summer-type HP. No patient had characteristics of epithelioid cell granuloma.

In both humidifier lung and summer-type HP, TBLB specimens showed alveolitis in all patients. However, there was no evidence of obvious cellular chronic bronchiolitis in TBLB specimens in all patients, because it was difficult to obtain sufficient bronchiolocentric area due to the small size of TBLB specimens. Thus, the pathological pattern was classified as indeterminate in all patients based on the GL for HP.

3.6 Guideline-based diagnosis of humidifier lung and summer-type HP

HRCT classification, precipitating IgG antibodies, exposures, pathological classification BALF lymphocyte count ratio, and total grade of confidence of HP diagnosis in all patients are shown in Figure 4. Definite or high level of confidence is depicted in dark green, while low level of confidence is highlighted in yellow. HRCT patterns were classified as typical HP in 5 (22%) and compatible with HP in 18 (78%) patients with humidifier lung and classified as typical HP in 17 (85%) and compatible with HP in 3 (15%) patients with summer-type HP. All patients with humidifier lung showed a clear correlation with exposure. Precipitating antibodies to *T. asahii* were confirmed present in all patients with summer-type HP. The percentage of patients with BALF lymphocyte count ratio of more than 20% was 15/19 (78.9%) in humidifier lung and 18/18 (100%) in summer-type HP. In both humidifier lung and summer-type HP, TBLB specimens showed cellular interstitial pneumonia (alveolitis) in all patients. However, there was no evidence of obvious cellular chronic bronchiolitis and granulomatous inflammation. Thus, the pathological pattern was classified as indeterminate in all patients based on GL for HP classification. The confidence level for the diagnosis of HP was definite in 3 (13.0%), moderate in 14 (60.9%), and low in 6 (26.1%) patients with humidifier lung and definite in 12 (60%), high in 3 (15%), and moderate in 5 (25%) patients with summer-type HP (Fig. 5).

4. Discussion

A few reports have suggested characteristic clinical and radiological differences between humidifier lung and summer-type HP [15,16]. These differences might depend on the nature or amount of inhaled

causative antigens and the duration of inhalation. We hypothesize that it is difficult to diagnose humidifier lung with high confidence using the GL for HP. However, few studies have carefully evaluated the utility of these guidelines for diagnosing humidifier lung and summer- type HP.

In our study, the diagnostic confidence for HP based on HRCT differed significantly between summer-type HP and humidifier lung. In the GL for HP, HRCT pattern was classified as typical and compatible for non-fibrotic HP according to specific HRCT findings [1]. Typical HP pattern consists of diffusely distributed HRCT findings including lung infiltration plus at least one HRCT abnormality suggestive of small airway disease. HRCT findings of small airway disease include ill-defined centrilobular nodules on inspiratory images and air trapping on expiratory images. These parenchymal patterns are usually bilateral and symmetric with a diffuse distribution, both axially and craniocaudally. A combination of parenchymal abnormalities and features of small airway disease is highly suggestive of nonfibrotic HP. In our study, most summer-type HP patients had parenchymal abnormalities and features of small airway disease, such as ill-defined centrilobular nodules, on HRCT. Therefore, many summer-type HP cases were classified as typical HP on HRCT.

Some of the patients with humidifier lung had nonspecific features but also had compatible HRCT findings, as compared with summer-type HP. Many cases of humidifier lung had parenchymal abnormalities such as uniform and subtle GGO and airspace consolidation, but did not have features of small airway disease such as ill-defined centrilobular nodules. Therefore, many patients with humidifier lung were classified as compatible with HP on HRCT. Consolidation on chest HRCT might be attributable to strong inflammatory reaction, including lung injury due to exposure to high levels of antigen and/or endotoxin [17-20].

For patients with newly identified interstitial lung disease for whom the differential diagnosis includes nonfibrotic HP, the GL for HP recommend BAL with lymphocyte cellular analysis. In our study, the percentage of patients with a BALF lymphocyte count ratio of more than 20% was 15/19 (78.9%) in those with humidifier lung and 19/19 (100%) in those with summer-type HP. Furthermore, in humidifier lung, the increase in BALF neutrophil fraction was greater than that for summer-type HP [15, 16]. Most HP patients, including those with summer-type HP, exhibit increased BAL T lymphocytes, predominantly $CD8^+$ lymphocytes, thus decreasing the CD4/CD8 ratio. However, CD4/CD8 ratio is higher in farmers' lung indicating that BAL lymphocyte phenotypes vary depending on the type of HP [1-5, 21-23]. Few studies of humidifier lung have evaluated BAL lymphocyte phenotypes [13, 15, 16]. They reported a significantly higher CD4/CD8 ratio for humidifier lung than for summer-type HP, which is consistent with our results. The reasons for these differences in WBC fractions and BAL lymphocyte phenotypes in HP are unclear and as mentioned above, may be attributed to the nature or amount of inhaled causative antigens and endotoxins.

In our study, diagnostic confidence for HP based on histopathological criteria did not differ between summer-type HP and humidifier lung. In the GL for HP, histopathological diagnostic confidence for nonfibrotic HP requires the presence of the following typical histopathological features: 1) Cellular

interstitial pneumonia accentuated around small airways (bronchiolocentric) accompanied by 2) Chronic cellular bronchiolitis, 3) A distinctive pattern of granulomatous inflammation, and 4) No histopathological features suggestive of a more likely alternative. The term indeterminate HP refers to cases where either cellular bronchiolocentric interstitial pneumonia or an otherwise unexplained chronic cellular bronchiolitis is present, but without the characteristic granulomatous inflammation [1]. Yet, in our study, the histopathological features in both humidifier lung and summer-type HP were classified as indeterminate in all patients. TBLB specimens showed cellular interstitial pneumonia (alveolitis) in all patients. There was no evident cellular chronic bronchiolitis. This is because of the difficulty in obtaining specimens with adequate bronchiolocentric area from TBLB. Therefore, we could not obtain sufficiently-sized TBLB specimens in the bronchiolocentric area to facilitate an accurate diagnosis of cellular bronchiolitis.

The GL for HP make no recommendations or suggestions for or against transbronchial lung cryobiopsy (TBLC) for patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP. Several studies reported higher diagnostic yield with TBLC than with TBLB, although the incidence of bleeding was also higher with TBLC [24, 25]. TBLC allows for obtaining specimens with adequate bronchiolocentric area. Wider use and improved safety of TBLC in the future would facilitate a more straightforward pathological evaluation of bronchiolocentric area, and more accurate pathological diagnosis of nonfibrotic HP.

The GL for HP provide robust criteria for establishing a diagnosis of HP. This is based on the incorporation of HRCT imaging, exposure assessment, BAL lymphocytosis, and histopathological features. In our study, 75% of summer-type HP patients were diagnosed with definite or high confidence, even though the pathological pattern was indeterminate, based on typical HRCT findings, increased BALF lymphocytosis, and the presence of precipitating *T. asahii* antibodies. However, only 13% of patients with humidifier lung were definitively diagnosed as HP, based on nonspecific features. But these could be compatible with nonfibrotic HP HRCT findings and the increased BALF neutrophil fraction. Thus, a unique set of criteria might be preferred for the accurate diagnosis of humidifier lung.

Limitations

This was a single-center retrospective study with a small sample size. A large-scale multicenter study is needed to confirm these findings as to whether humidifier lung and summer-type HP can be diagnosed with the GL for HP.

5. Conclusion

Using the GL for HP, diagnostic confidence was moderate to low for many humidifier lung patients, but was definite-to-high for patients with summer-type HP. Therefore, a unique set of criteria is beneficial for the diagnosis of humidifier lung.

Declarations

Ethical approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Toho University Omori Medical Center in April 2022 (project approval number M20221). Considering the nature of the retrospective study, the informed consent was waived by the IRB because of the anonymized patient data. The study protocol was performed in accordance with the relevant guidelines.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

We declare that we have no conflict of interest.

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Author contributions: S.S. served as principal author and had access to, and takes responsibility for, the integrity of the data and the accuracy of the data analysis. S.S. and S.H. contributed to the design of the study; S.S., M.M., S.H., T.I., Y.T., Y.U., K.K., N.U., M.S., S.M., and K.I. contributed to data collection; S.S., T.I., Y.N., and S.H. contributed to interpretation of the study; S.S., M.M., T.I., and S.H. contributed to the study analysis; and A.K., S.S., T.I., H.S., Y.U., Y.N., and S.H. contributed to evaluation of HRCT images. All authors were involved in drafting and revising this report and gave their final approval of the version to be published. All authors vouch for the accuracy of the content included in the final report.

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Tables

Table 1. Characteristics of patients with humidifier lung and summer-type hypersensitivity pneumonitis (HP)

	Humidifier lung (n=23)	Summer-type HP (n=20)	P value
Age (y)	68.0±14.4	57.4±17.6	0.035*
Male, n (%)	17 (70.1)	9 (47.3)	0.118
Body height (cm)	160±7.85	162±9.97	0.477
Body weight (kg)	58.3±7.81	59.6±15.0	0.817
Body mass index (kg/m^2)	21.5±6.2	18.8±9.5	0.975
Smoking (Current/Former/Never)	1/11/11	0/10/10	0.606
Smoking index	498.2±811.3	246.5±385.0	0.639
Season at the time of first hospital visit (Mar-May/Jun-Aug/Sep-Nov/ Dec-Feb)	4/0/1/18	1/10/7/1	0.003*
Symptoms			
mMRC	2.0±0.4	2.5±0.9	0.281
Dyspnea, n (%)	18 (78.2)	17(85.0)	0.310
Cough, n (%)	20 (87.0)	15 (75.0)	0.772
Fever, n (%)	17 (73.9)	8 (40.0)	0.248
Sputum, n (%)	11 (47.8)	6 (30.0)	0.642

*mMRC: Modified Medical Research Council Dyspnea Scale

Table 2: Laboratory and pulmonary function test results for patients with humidifier lung and summer-type hypersensitivity pneumonitis (HP)

	Humidifier lung (n=23)	Summer-type HP (n=20)	P value	
Blood tests				
White blood cells (/μL)	13.5±6.5× 10^3	7.5±2.3 × 10^3	0.003	*
Eosinophils (%)	2.4±3.1	3.1±3.4	0.042	*
Lymphocytes (%)	13.2±7.2	22±13.1	0.008	*
Neutrophils (%)	79.4±9.5	68.0±13.7	0.003	*
CRP (mg/dL)	8.0±6.5	2.1±2.7	0.004	*
LDH (U/L)	258.5±69.8	294±89.0	0.346	
KL-6 (U/mL)	593.4±396.7	2107.7±2029.7	0.001	*
SP-D (ng/mL)	162.4±156.7	579.8±505.8	0.001	*
SP-A (ng/mL)	99.7±52.0	95.7±62.2	0.812	
Arterial blood gas analysis				
PaO_2 (Torr)	69.4±16.0	72.2±14.3	0.551	
$PaCO_2$ (Torr)	37.8±4.2	38.2±4.7	0.597	
PaO_2/FiO_2 ratio	323.9±100.4	331±88.0	0.422	
Aa-DO_2 (Torr)	29.6±15.7	29.8±14.0	0.851	

KL-6: Krebs von der Lungen-6; SP-D: surfactant protein D; SP-A: surfactant protein A; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Table 3: High-resolution computed tomography (HRCT) findings in patients with humidifier lung and summer-type hypersensitivity pneumonitis (HP)

Chest HRCT findings	Humidifier lung (n=23)	Summer-type HP (n=20)	P value	
Ground-glass opacity, n (%)	22 (95.6)	19 (95.0)	0.806	
Centrilobular nodule, n (%)	7 (30.4)	12 (65.0)	0.026	*
Peribronchovascular or subpleural nonsegmental consolidation, n (%)	12 (52.1)	1 (5.0)	0.002	*
Mosaic attenuation, n (%)	12 (52.2)	15 (75.0)	0.115	
Subpleural curve linear opacity, n (%)	4 (17.4)	5 (25.0)	0.363	

Table 4: Bronchoalveolar lavage fluid findings in patients with humidifier lung and summer-type hypersensitivity pneumonitis (HP)

	Humidifier lung (n=15)	Summer-type HP (n=19)	P value	
Total cell count, n /mL	$3.0\pm2.3 \times 10^5$	$3.3\pm2.4 \times 10^5$	0.60	
Neutrophils (%)	22.1±25.6	8.1±13.6	0.16	
Lymphocytes (%)	37.3±20.1	69.0±22.6	<0.001	*
Eosinophils (%)	9.47±19.0	3.1±2.8	1.00	
Macrophages (%)	31.2±22.2	20.0±19.6	0.05	
CD4 (%)	51.2±11.9	32.9±17.9	0.002	*
CD8 (%)	34.7±9.4	60.8±21.0	0.002	*
CD4/CD8 ratio	1.7±1.2	0.8±0.9	0.003	*

Table 5: Pathological findings in patients with humidifier lung and summer-type hypersensitivity pneumonitis (HP)

	Humidifier lung (n=9)	Summer-type HP (n=15)	P-value	
Alveolitis n (%)	9 (100)	15 (100)	1.000	
Severe alveolitis n (%)	1 (11)	10 (66.7)	0.013	*
Organization n (%)	4 (44.4)	11 (73.3)	0.212	
Eosinophilia n (%)	2 (22.2)	3 (20)	1.000	
Granuloma n (%)	0 (0)	2 (13.3)	0.511	
Alveolar epithelial cell hyperplasia n (%)	8 (88.9)	14 (93.3)	1.000	
Severe alveolar epithelial cell hyperplasia n (%)	2 (22.2)	8 (53.3)	0.134	
Giant cells n (%)	0 (0)	6 (40)	0.052	
Intra-alveolar macrophages n (%)	1 (11.1)	10 (66.7)	0.013	*
Cellular chronic bronchiolitis n (%)	0 (0)	0 (0)	1.000	

The severity of alveolitis and alveolar epithelial cell hyperplasia was classified as −, +, and 2+, and a classification of 2+ was considered severe.

Figures

Figure 1

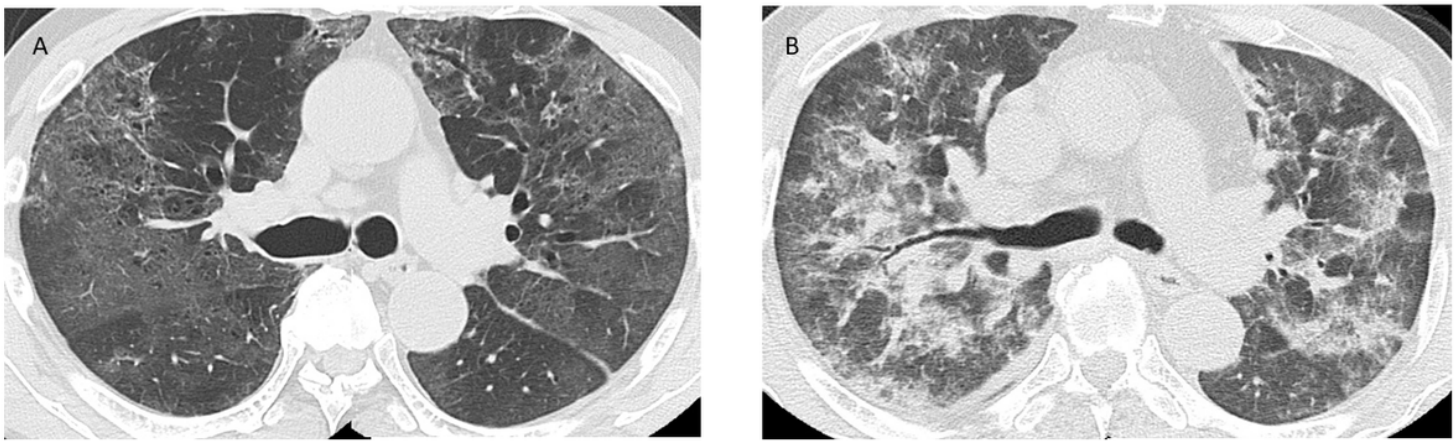


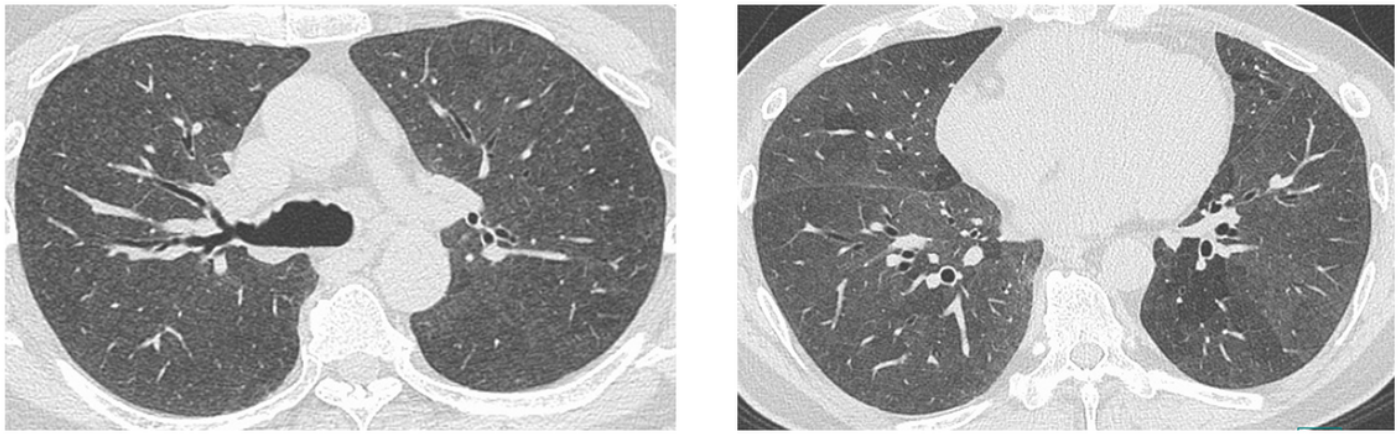
Figure 1

Representative chest HRCT findings for humidifier lung.

A) Diffuse faint ground-glass opacity and mosaic attenuation, without poorly-defined centrilobular micronodules.

B) Diffuse nonsegmental peribronchovascular consolidation bilaterally, with intralobular septal thickening—an unusual finding in summer-type HP.

Figure 2

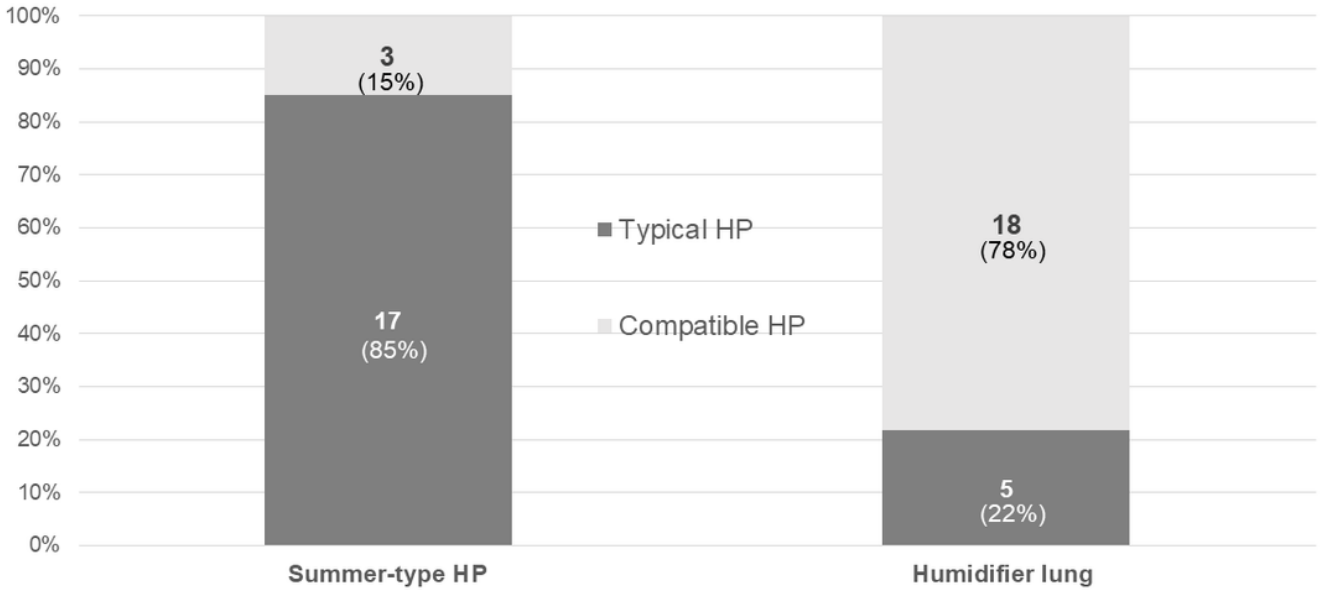


Representative chest HRCT scan for typical summer-type HP showing diffuse ground-glass opacities with poorly defined micronodules and mosaic attenuation.

Figure 2

Representative chest HRCT scan of typical summer-type HP showing diffuse ground-glass opacity with poorly-defined micronodules and mosaic attenuation.

Figure 3



	Typical HP	Compatible HP
Summer-type HP	17	3
Humidifier lung	5	18

Figure 3

HRCT pattern according to the Guidelines for HP criteria for summer-type HP and humidifier lung.

Figure 4

High

Low

Confidence level

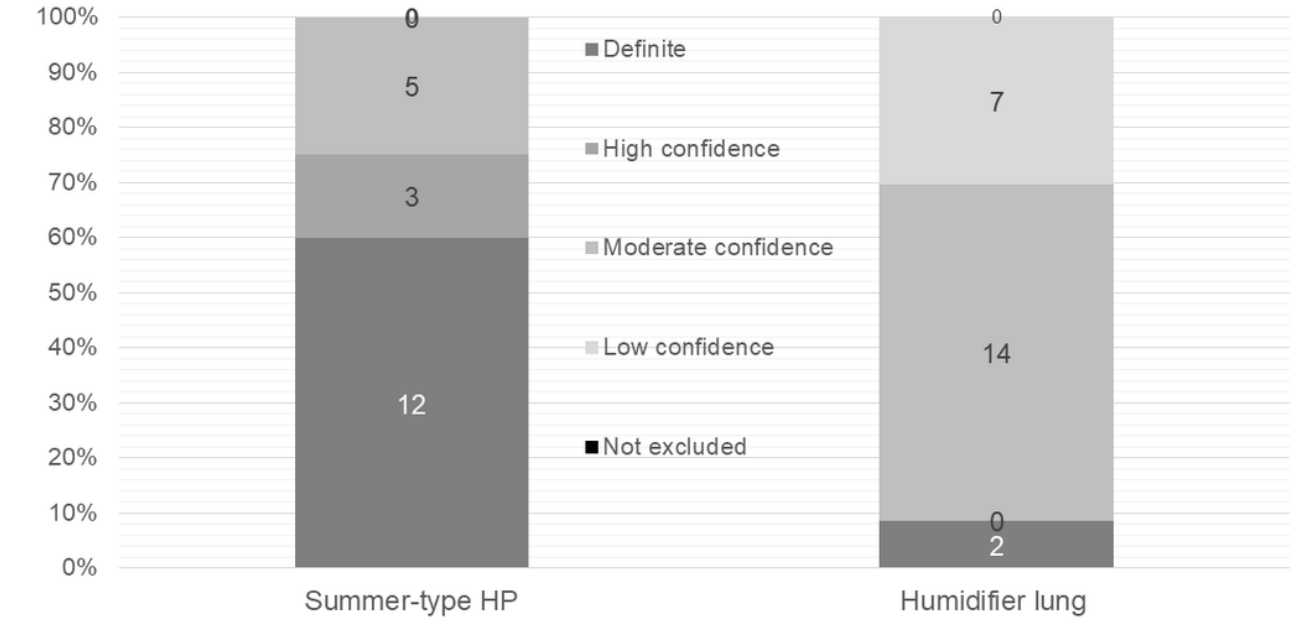
Summer-type HP	HRCT classification	*T. asahii* antibody	% of BALF Lymphocytes	Pathological classification	Total grade of confidence of HP diagnosis
Case 1	Typical	Positive	89	Indeterminate	Definite
2	Typical	Positive	69	Indeterminate	Definite
3	Typical	Positive	88	Indeterminate	Definite
4	Typical	Positive	83	Indeterminate	Definite
5	Typical	Positive	85	Indeterminate	Definite
6	Typical	Positive	77	Indeterminate	Definite
7	Typical	Positive	74	Indeterminate	Definite
8	Typical	Positive	90	Indeterminate	Definite
9	Typical	Positive	85	Indeterminate	Definite
10	Typical	Positive	47	Indeterminate	Definite
11	Typical	Positive	23	Indeterminate	Definite
12	Typical	Positive	62	Indeterminate	Definite
13	Typical	Positive	40	N/A	High confidence
14	Typical	Positive	83	N/A	High confidence
15	Typical	Positive	55	N/A	High confidence
16	Typical	Positive	N/A	N/A	Moderate confidence
17	Typical	Positive	N/A	Indeterminate	Moderate confidence
18	Compatible	Positive	71	Indeterminate	Moderate confidence
19	Compatible	Positive	76	N/A	Moderate confidence
20	Compatible	Positive	65	N/A	Moderate confidence
Humidifier lung	**HRCT classification**	**Exposure**	**% of BALF Lymphocytes**	**Pathological classification**	**Total grade of confidence of HP diagnosis**
Case 1	Typical	Positive	59	Indeterminate	Definite
2	Typical	Positive	58	Indeterminate	Definite
3	Typical	Positive	27	Indeterminate	Definite
4	Typical	Positive	15	Indeterminate	Moderate confidence
5	Typical	Positive	15	Indeterminate	Moderate confidence
6	Compatible	Positive	37	Indeterminate	Moderate confidence
7	Compatible	Positive	78	Indeterminate	Moderate confidence
8	Compatible	Positive	44	Indeterminate	Moderate confidence
9	Compatible	Positive	34	Indeterminate	Moderate confidence
10	Compatible	Positive	43	Indeterminate	Moderate confidence
11	Compatible	Positive	56	Indeterminate	Moderate confidence
12	Compatible	Positive	44	Indeterminate	Moderate confidence
13	Compatible	Positive	26	Indeterminate	Moderate confidence
14	Compatible	Positive	20	Indeterminate	Moderate confidence
15	Compatible	Positive	69	N/A	Moderate confidence
16	Compatible	Positive	47	N/A	Moderate confidence
17	Compatible	Positive	31	N/A	Moderate confidence
18	Compatible	Positive	7	Indeterminate	Low confidence
19	Compatible	Positive	10	Indeterminate	Low confidence
20	Compatible	Positive	N/A	N/A	Low confidence
21	Compatible	Positive	N/A	N/A	Low confidence
22	Compatible	Positive	N/A	N/A	Low confidence
23	Compatible	Positive	N/A	N/A	Low confidence

N/A: not available

Figure 4

Diagnosis of hypersensitivity pneumonia with the GL for HP. Based on incorporation of HRCT imaging, exposure assessment, BAL lymphocytosis, and histopathological features.

Figure 5



	Definite	High confidence	Moderate confidence	Low confidence	Not excluded
Summer-type HP	12	3	5	0	0
Humidifier lung	2	0	14	7	0

Figure 5

Confidence level for the diagnosis of HP in patients with humidifier lung and patients with summer-type HP.