



CORRESPONDENCE

Features of humidifier lung and comparison with summer-type hypersensitivity pneumonitis

To the Editors:

Humidifier lung is a phenotype of hypersensitivity pneumonitis (HP) caused by the inhalation of humidifier vapours. A recent study comparing humidifier lung with summer-type HP reported several distinct features, including lower serum Krebs von den Lungen-6 (KL-6) levels, less common centrilobular ground-glass

nodules on computed tomography scan and a higher ratio of CD4⁺ to CD8⁺ cells in bronchoalveolar lavage.¹ However, the features and mechanisms of humidifier lung are not well characterized. Indicators for discrimination of humidifier lung from other phenotypes of HP are uncertain. Here, we report more characteristics of histopathological findings and a diagnostic predictor for humidifier lung compared to summer-type HP, which is the most common phenotype of HP in Japan.^{1,2}

Among 82 adult patients hospitalized for HP at Fukujiji Hospital from April 1999 to March 2018, 7 patients with humidifier lung (18.3%) and 26 patients with summer-type HP (43.3%) were

Table 1 Baseline characteristics of the patients in this study

	Humidifier lung (<i>n</i> = 7)	Summer-type HP (<i>n</i> = 26)	<i>P</i> -value
Age, median (IQR), years	49.0 (43.5–53.0)	56.0 (45.3–66.5)	0.332
Sex (male/female)	6/1	7/19	0.008
Comorbidity, <i>n</i> (%)	3 (85.7)	17 (65.4)	0.397
Underlying respiratory diseases, <i>n</i> (%)	4 (57.1)	5 (19.2)	0.320
Smoking history, <i>n</i> (%) [†]	5 (83.3)	6 (27.3)	0.022
Duration from symptom onset to hospital visit, median (IQR), days [‡]	6.0 (3.0–17.5)	30.0 (17.8–57.5)	0.006
Symptom			
Fever, <i>n</i> (%)	7 (100)	11 (42.3)	0.010
Cough, <i>n</i> (%)	3 (42.9)	20 (76.9)	0.161
Desaturation, <i>n</i> (%)	4 (57.1)	15 (57.7)	1.000
Laboratory findings			
WBC, median (IQR), cells/ μ L	13 460 (7600–19 350)	8880 (8070–10 213)	0.288
CRP, median (IQR), mg/dL	5.23 (2.90–7.00)	1.50 (0.60–2.98)	0.027
LDH, median (IQR), IU/L [§]	192 (163–208)	255 (218–358)	0.006
KL-6, median (IQR), U/L [¶]	316 (303–587)	1690 (1093–3385)	<0.001
Typical HRCT patterns of HP, <i>n</i> (%)	4 (57.1)	16 (61.5)	1.000
Bronchoalveolar lavage fluid			
Lymphocytes, median (IQR), %	53.9 (46.5–63.4)	72.5 (51.1–76.7)	0.101
CD4/8 ratio, median (IQR)	2.6 (1.7–4.4)	0.3 (0.2–0.6)	<0.001
Lung biopsy specimens ^{††}			
Granuloma, <i>n</i> (%)	0 (0.0)	9 (56.3)	0.045
Alveolitis, <i>n</i> (%)	4 (80.0)	14 (87.5)	1.000
Steroid therapy, <i>n</i> (%)	3 (42.9)	16 (61.5)	0.442

[†]Humidifier lung *n* = 6, summer-type HP *n* = 22.

[‡]Humidifier lung *n* = 7, summer-type HP *n* = 22.

[§]Humidifier lung *n* = 7, summer-type HP *n* = 7.

[¶]Humidifier lung *n* = 10, summer-type HP *n* = 23.

^{††}Humidifier lung *n* = 5, summer-type HP *n* = 16.


CD4/8 ratio, ratio of CD4⁺ to CD8⁺ cells; CRP, C-reactive protein; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; WBC, white blood cell.

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enrolled, 22 patients with unfulfilled diagnostic criteria of HP³ and 27 patients with other phenotypes of HP were excluded (15 patients with various exposures to fungi contaminating a house, 4 patients with bird fancier's lung and 8 patients with unknown origin). The diagnosis of HP was based on criteria outlined in the official American Thoracic Society, Japanese Respiratory Society and Asociación Latinoamericana del Tórax (ATS/JRS/ALAT) clinical practice guideline 2020.³ The baseline characteristics of the patients are shown in Table 1.

The humidifier lung group showed faster disease progression (shorter duration from symptom onset to hospital visit) than the summer-type HP group (median (interquartile range (IQR)): 6.0 (3.0–17.5) vs 30.0 days (17.8–57.5), $P = 0.006$). Granulomas in histopathological findings were significantly less common in humidifier lung patients than in summer-type HP patients ($n = 0$ (0.0%) vs $n = 9$ (56.3%), $P = 0.045$). Serum KL-6 levels were significantly lower in humidifier lung patients than in summer-type HP patients (median (IQR): 316 (303–587 U/mL) vs 1690 U/mL (1093–3385 U/mL), $P < 0.001$). The area under the receiver operating characteristic curve for serum KL-6 for distinguishing humidifier lungs from summer-type HP was 0.887. When the cut-off value of serum KL-6 was less than 674 U/mL, the sensitivity, specificity and odds ratio (OR) were 85.7%, 95.7% and 83.4 (95% CI: 5.3–5909.3), respectively.

Generally, the mechanism of HP other than humidifier lung is extrinsic allergic alveolitis with type III (immune complex-mediated) or IV (delayed) granulomas.⁴ However, antigens associated with humidifier lung have been reported in patients exposed to not only various bacteria and fungi but also endotoxins.^{4,5} The mechanism of humidifier lung might be different from the other phenotypes of HP because of less frequent granuloma formation, faster disease progression and lower KL-6 levels, as we have shown. We believe that one of the different mechanisms is related to exposure to endotoxins; however, there is no report demonstrating the presence of endotoxins in humidifier vapours. Therefore, examination of both humidifier water and vapours is warranted in future.

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