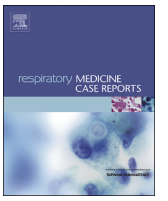
Respiratory Medicine Case Reports 51 (2024) 102061

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Diffusely distributed centrilobular micronodules and branching opacities as the main chest computed tomography manifestations in a patient with humidifier lung

Chinatsu Nakane, Takahiro Teshima, Ryosuke Otake, Emiko Nakagawa, Ei Kishimoto, Kosuke Suzuki, Ryunosuke Inaba, Yurina Murakami, Yoichiro Aoshima, Koji Nishimoto, Sayomi Matsushima, Masanori Harada, Shiro Imokawa *

Division of Respiratory Medicine, Iwata City Hospital, Iwata, 438-8550, Japan

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Hypersensitivity pneumonitis
Organizing pneumonia
Transbronchial lung biopsy

ABSTRACT

We report a 60-year-old man with humidifier lung showing diffusely distributed centrilobular micronodules and branching opacities on chest computed tomography (CT). Fever and dyspnea occurred 2 months after using an ultrasonic humidifier. KL-6 and SP-D were within normal ranges. Bronchoalveolar lavage showed elevated lymphocytes (53 %) and histological findings of transbronchial lung biopsy demonstrated organizing pneumonia. His condition improved after cessation of the humidifier. A provocation test exhibited a positive response to the humidifier. Humidifier lung should be considered as a differential diagnosis in patients with these CT findings. Detailed clinical, pathological and microbiological examinations are needed to exclude other diseases.

1. Introduction

Various diseases, including mycobacterial infections, bacterial and viral infections, diffuse pan-bronchiolitis, and connective tissue diseases-associated follicular bronchiolitis show diffusely distributed centrilobular micronodules and branching opacities on chest computed tomography (CT) [1]. The micronodules usually associate with nonfibrotic hypersensitivity pneumonitis (HP) are typically poorly defined and associated with ground glass opacities and/or consolidations [2,3]. Humidifier lung is a type of home environment HP [4], and it has been reported that these centrilobular micronodules are less common in humidifier lung than in summer-type HP [5]. We herein describe a case of humidifier lung presenting with diffusely distributed centrilobular micronodules and branching structures as the main chest CT manifestations.

2. Case presentation

A 60-year-old man was referred to our hospital for evaluation of fever and dyspnea. He was a former-smoker (20 pack-years), and had a medical history of parapsoriasis treated with etretinate. His symptoms occurred 2 months after the use of an ultrasonic humidifier. No crackles were audible on auscultation. Chest CT before admission showed diffusely distributed centrilobular micronodules (2–3 mm in diameter) and branching structures that did not extend to the pleural surface, some resembling “tree-in-bud opacities”

* Corresponding author. Division of Respiratory Medicine, Iwata City Hospital, 512-3, Ookubo, Iwata, 438-8550, Japan.
E-mail address: imokawas@hospital.iwata.shizuoka.jp (S. Imokawa).

https://doi.org/10.1016/j.rmcr.2024.102061
Received 16 November 2023; Accepted 30 May 2024
Available online 3 June 2024

(Fig. 1). Laboratory examination revealed a white blood cell count of 25,700/μL and C-reactive protein of 11.53 mg/dL. Serum KL-6 (327 U/ml) and SP-D (93.1 ng/ml) levels were within the normal ranges. He was admitted for further evaluation.

Pulmonary function tests revealed moderately reduced diffusing capacity (% single-breath carbon monoxide diffusing capacity 58.6 %), but the forced vital capacity (3.31 L, 90.4 % of predicted) and forced expiratory volume in 1 (3.12 L, 102.6 % of predicted) were within normal ranges. Bronchoalveolar lavage fluid (BALF) from the right B^5_a revealed increased numbers of total cells (2.44×10^5/ml BALF), lymphocytes (53.0 %), neutrophils (29.8 %), and eosinophils (6.6 %). The CD4/CD8 ratio of BALF lymphocytes was 1.41. No pathogenic organisms were detected in the BALF. A transbronchial lung biopsy specimen showed intra-luminal organization in the respiratory bronchiole and alveolar ducts without granulomas (Fig. 2).

The patient's condition and his laboratory and chest roentgenogram findings improved immediately after stopping use of the humidifier. Based on the clinical course, we suspected HP associated with humidifier use (humidifier lung). He underwent a provocation test using this humidifier [6] with written informed consent. Briefly, the humidifier (Fig. 3a and b) was operated in a hospital room measuring approximately 8 m^2 with the windows and door closed. The patient was exposed to the humidifier mist for 1 h. Seven hours after humidifier use, he developed fever (38.3 °C), dry cough, dyspnea, and fatigue. Laboratory examination revealed peripheral leukocytosis (16,200/μL) and elevated C-reactive protein (9.14 mg/dL). His PaO_2 was also decreased (59.5 mmHg). Chest roentgenograms were not changed before and after the provocation test. He was accordingly diagnosed with humidifier lung. His symptoms and laboratory findings improved spontaneously within three days.

Several microorganisms were isolated from the humidifier water (Fig. 3c), including *Acinetobacter* species, *Chryseobacterium* species, *Brevundimonas albigilva, Pseudomonas alcaligenes, Cladosporium* species, *Candida guilliermondii,* and *Candida parapsilosis*. Serum antibody against *Trichosporon asahii* was negative. The humidifier water also contained high concentrations of endotoxin (more than 1000 pg/dL) and β-D glucan (10,879.6 pg/ml). A lymphocyte stimulation test for the humidifier water was negative.

3. Discussion

Chest CT findings in non-fibrotic HP demonstrate diffuse parenchymal infiltration with or without abnormalities suggestive of small airway disease [3]. The former includes ground-glass opacities and mosaic attenuation, and the latter includes ill-defined, small (under 5mm in diameter) centrilobular nodules on inspiratory images [3]. Some types of HP (Japanese summer-type HP [7] or pool-water spray and fountain associated HP [8]) demonstrate diffusely distributed, ill-defined centrilobular nodules 2–3 mm in diameter without parenchymal abnormalities on chest CT. There have been few reports of the chest CT findings of humidifier lung; however, Sakamoto et al. [5] notably reported that centrilobular micronodules were less common in patients with humidifier lung. In our case, diffusely distributed centrilobular micronodules and branching structures were the main CT manifestations.

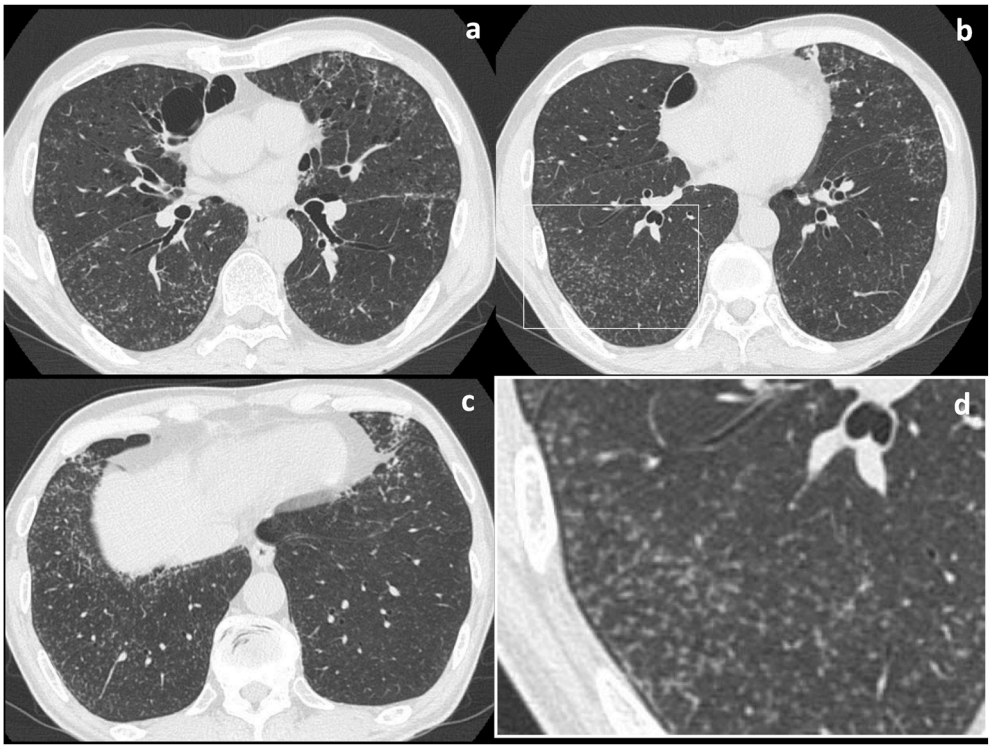


Fig. 1. a-c. Serial chest computed tomography images showing diffusely distributed centrilobular nodules and branching structures away from the pleura and interlobular septa. **d**. Enlarged area in **b**.

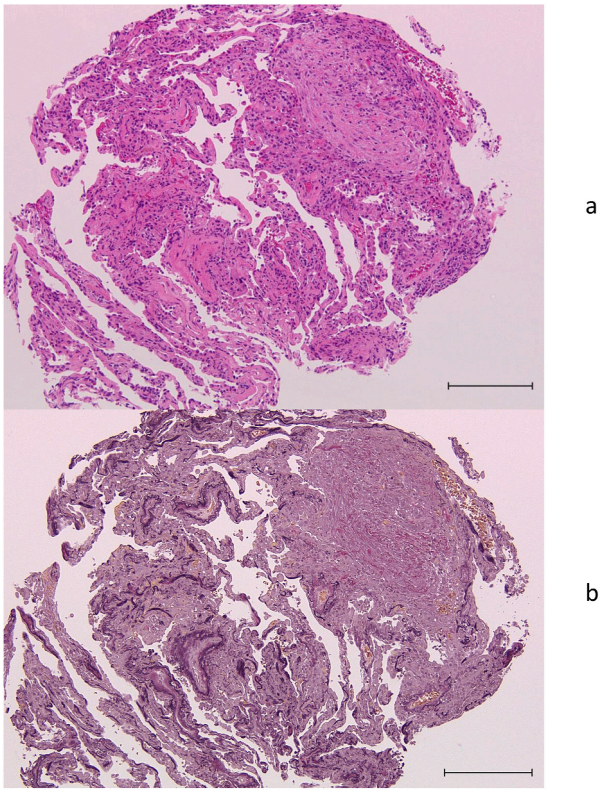


Fig. 2. Transbronchial lung biopsy specimen showing intra-luminal organization in the respiratory bronchiole to alveolar duct without granulomas (**a, b**). Alveolar septal thickening by scant inflammatory cells is seen (**a**). a: Hematoxylin and eosin staining, b: Elastica van Gieson staining, bar indicates 200 μm.

Fig. 3. a. Ultrasonic humidifier used by the patient. Asterisk shows water reservoir. **b.** Aerosol dispersion nozzles (arrows). **c.** Humidifier water and ultrasonic generator in the tank. There was grayish residue in the water (arrow heads).

Normal bronchioles have a diameter of under 1 mm and a wall thickness of under 0.1 mm [1]. In patients with mycobacterial infections, filling of the intraluminal airways with inspissated secretions or mucus plugs results in bronchiolar distension and increased density, allowing the direct visualization of small airways as micronodules and branching opacities on chest CT [1]. In patients with diffuse pan-bronchiolitis, the accumulation of foamy cells accompanied by infiltration of lymphocytes and plasma cells in the peribronchiolar area corresponds to these micronodules [9], and in patients with follicular bronchiolitis, these findings presumably represent abundant lymphoid follicles distributed along the bronchiole [10]. In the current patient, the respiratory bronchiole to the alveolar duct was filled with fibrous organizing tissues, and we therefore speculated that the centrilobular micronodules and branching structures corresponded to these pathological findings; however, the tissue samples obtained by transbronchial lung biopsy were not sufficient to examine the correlation between the CT and pathologic findings.

Some previous reports have suggested that endotoxins may induce humidifier lung [11,12]. Endotoxins are toxins that occur on the cell wall of Gram-negative bacteria [13,14]. In this case, endotoxin levels in the humidifier water were elevated (more than 1000 pg/dL). Organizing pneumonia is one of the histopathological findings of lung injury caused by various toxic insults [15]. We therefore speculated that, in addition to type III and type IV allergic reactions, endotoxin reaction might also contribute to the pathogenesis of lung disease in our patient, as reported previously [11,12].

It is unclear why the lung disease in the present case was mainly localized to the small airways. One possible reason may be the size of the inhaled particles; ultrasonic humidifiers generate water droplets of 0.5–3.0 μm [16,17], some of which may coalesce to form doublets with a diameter of 3.0–5.0 μm [17], and maximal retention of inhaled particles of 3.0–5.0 μm may occur in the small air ways [18]. Inhaled water droplets containing bacterial endotoxins can cause neutrophilic inflammation through the release of complement cascade component C5a and interleukin-8 from bronchial epithelial cells [13], inducing tissue injury mainly around the small air-ways. Other factors may contribute to the particle size such as structure of the humidifier, temperature and humidity in the atmosphere, microorganisms in the humidifier, and et al., but we could not find any evidence. Further investigations are needed to clarify them.

Although water droplets generated by ultrasonic humidifiers range from 0.5 to 5 μm, centrilobular micronodules are rare in patients with humidifier lung [5], suggesting that other factors may contribute to these CT findings. There is considerable interindividual variability in the extents of both the clinical and inflammatory responses to endotoxin inhalation [11]. A polymorphism in the TLR4 gene causes differences in endotoxin responsiveness in humans [19], which is also affected by polymorphisms in the genes encoding the pro-inflammatory lipopolysaccharide-induced cytokine tumor necrosis factor-α and the lipopolysaccharide receptor CD-14 [13]. These above host factors may have contributed to the pathogenesis in our patient. Moreover, various microorganisms, including Gram-negative bacteria, fungi, and non-tuberculous mycobacteria, have been implicated in the development of humidifier lung [6,12,20,21]. In the current case, various fungi and bacteria were isolated from the humidifier water. Although the precise mechanisms are unknown, many factors, such as the causal antigens, particle size, and variability in endotoxin sensitivity, may thus have contributed to the pathogenesis of lung disease in this patient.

4. Conclusion

Humidifier lung should be included in the differential diagnosis in patients with diffusely distributed centrilobular micronodules and branching opacities without parenchymal abnormalities. Detailed clinical, pathological and microbiological examinations are needed to exclude other diseases.

Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sections.

Author contributions

CN, YM and SM managed the patient. CN, YM, SM, MH, and SI created the figures, and collected the laboratory data. CN, MH and SI wrote the manuscript. CN, TT, RO, EN, EK, KS, RI, YM, YA, KN, SM, MH, and SI contributed to the discussion of the results and reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

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

Acknowledgements

We thank Susa Furness, PhD from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

References

[1] S. Raoof, A. Amchentsev, I. Vlahos, A. Goud, D.P. Naidichi, Pictorial essay: multinodular disease. A high-resolution CT scan diagnostic algorithm, Chest 129 (2006) 805–815.
[2] S.F. Silver, N.L. Muller, R.R. Miller, M.S. Lefcoe, Hypersensitivity pneumonitis: evaluation with CT, Radiology 173 (1989) 441–445.
[3] G. Raghu, M. Remy-Jardin, C.J. Ryerson, J.L. Myers, Vasakova M. KreuterM, E. Bargagli, J.H. Chung, B.F. Collins, E. Bendstrup, H.A. Chami, A. Chua, T.J. Corte, J.-C. Dalphin, S.K. Danoff, J. Diaz-Mendoza, A. Duggal, R. Egashira, T. Ewing, M. Gulati, Y. Inoue, A.R. Jenkins, K.A. Johannson, T. Johkoh, M. Tamae-Kakazu, M. Kitaichi, S.L. Knight, D. Koschel, D.J. Lederer, Y. Mageto, L.A. Maier, C. Matiz, F. Morell, A.G. Nicholson, S. Patolia, C.A. Pereira, E.A. Renzoni, M.L. Salisbury, M.

Selman, S.L.F. Walsh, W.A. Wuyts, Asociacion Latinoamericana de Torax, Am. J. Respir. Crit. Care Med. 202 (2020) e36–e69.
[4] X. Baur, J. Behr, M. Dewair, W. Ehret, G. Fruhmann, C. Vogelmeier, W. Weiss, V. Zinkernagel, Humidifier lung and humidifier fever, Lung 166 (1988) 113–124.
[5] S. Sakamoto, M. Furukawa, H. Shimizu, M. Sekiya, S. Miyoshi, Y. Nakamura, N. Urabe, T. Isshiki, Y. Usui, K. Isobe, Y. Takai, A. Kurosaki, K. Kishi, S. Homma, Clinical and radiological characteristics of ultrasonic humidifier lung and summer type hypersensitivity pneumonitis, Respir. Med. 174 (2020) 106196.
[6] T. Suda, A. Sato, M. Ida, H. Genma, H. Hayakawa, K. Chida, Hypersensitivity pneumonitis associated with home ultrasonic humidifier, Chest 107 (1995) 711–717.
[7] H. Nakata, K. Egashira, T. Tsuda, K. Hiraoka, M. Kido, High-resolution computed tomography of Japanese summer-type hypersensitivity pneumonitis, Clin. Imag. 15 (1991) 185–190.
[8] D.A. Lynch, C.S. Rose, D. Way, T.E. King, Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study, AJR 159 (1992) 469–472.
[9] M. Akira, F. Kitatani, L. Young-Sik, N. Kita, S. Yamamoto, T. Higashihara, S. Morimoto, J. Ikezoe, T. Kozuka, Diffuse panbronchiolitis: evaluation with high-resolution CT, Radiology 168 (1988) 433–438.
[10] S.J. Howling, D.M. Hansell, A.U. Wells, A.G. Nicholson, J.D.A. Flint, N.L. Muller, Follicular bronchiolitis: thin-section CT and histologic findings, Radiology 212 (1999) 637–642.
[11] H. Ohnishi, A. Yokoyama, H. Hamada, S. Manabe, R. Ito, A. Watanabe, H. Katayama, Y. Yasuhara, J. Ikezoe, J. Higaki, Humidifier lung: possible contribution of endotoxin-induced lung injury, Intern. Med. 41 (2002) 1179–1182.
[12] M. Shimoda, K. Morimoto, Y. Tanaka, K. Ohta, K. Yoshimori, Humidifier lung induced by endotoxin and various pathogens: characteristic differences from other phenotypes of hypersensitivity pneumonitis, Respir Med Case Rep 31 (2020) 101267.
[13] J. Thorn, The inflammatory response in humans after inhalation of bacterial endotoxin: a review, Inflamm. Res. 50 (2001) 254–261.
[14] O. Michel, Systemic and local airways inflammatory response to endotoxin, Toxicology 152 (2000) 25–30.
[15] A.L.A. Katzenstein, Diagnostic Atlas of Non-neoplastic Lung Disease. A Practical Guide for Surgical Pathologist, demosMedical Publisher, Inc., NewYork, 2016, pp. 85–114.
[16] B.A. Shapiro, R.A. Harrison, R.M. Racemarek, Humidity and aerosol therapy, in: B.A. Shapiro, R.A. Harrison, R.M. Racemarek, R.D. Cane (Eds.), Clinical Application of Respiratory Care, third ed., Year Book Medical Publisher, Inc., Chicago, 1985, pp. 90–109.
[17] C. Rodes, T. Smith, R. Crouse, G. Ramachandran, Measurements of the size distribution of aerosols produced by ultrasonic humidification, Aerosol. Sci. Technol. 13 (1990) 220–229.
[18] T.F. Hatch, Distribution and deposition of inhaled particles in respiratory tract, Bacteriol. Rev. 25 (1961) 237–240.
[19] N.C. Arbour, E. Lorenz, B.C. Schutte, J. Zabner, J.N. Kline, M. Jones, K. Frees, J.L. Watt, D.A. Schwartz, TLR4 mutations are associated with endotoxin hyporesponsiveness in humans, Nat. Genet. 25 (2000) 187–191.
[20] H. Utsugi, Y. Usui, F. Nishihara, M. Kanazawa, M. Nagata, *Mycobacterium gordonae*-induced humidifier lung, BMC Pulm. Med. 15 (2015) 108, https://doi.org/10.1186/s12890-015-0107-y.
[21] M. Shimoda, K. Morimoto, M. Hosoya, A. Osugi, S. Mitarai, Y. Tanaka, K. Fujiwara, K. Yoshimori, K. Ohta, Causative antigens of humidifier lung in vapor from a humidifier: a case report, Respir Med Case Rep 43 (2023) 101851.