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Case Report

Ultrasonic humidifier lung with a reversed halo sign: A case report ☆,☆☆

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ABSTRACT

The reversed halo sign was initially reported as a representative computed tomography scan finding of cryptogenic organizing pneumonia. Since then, however, it has been reported in various diseases and is now considered a nonspecific finding. However, there are no cases of humidifier lung with the reversed halo sign. An 82-year-old Japanese male patient presented with moving difficulties 48 days after starting darolutamide treatment for prostate cancer. He was admitted to the hospital due to acute pneumonia, which presented as bilateral extensive nonsegmental ground-glass opacities in the peripheral regions and extensive areas of ground-glass opacity with a circumferential halo of consolidation, with the reversed halo sign on computed tomography scan. After darolutamide discontinuation with the concomitant administration of antibiotics, the patient's pneumonia improved, and he was discharged from the hospital. However, within a few days, he was again admitted to the hospital due to pneumonia. He was found to have been using an ultrasonic humidifier at home and was then diagnosed with humidifier lung based on the bronchoscopy and provocative

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testing findings. Hence, ultrasonic humidifier lung should be considered as a differential diagnosis in patients presenting with the reversed halo sign, and a detailed medical history must be taken.

Introduction

Humidifier lung is a type of hypersensitivity pneumonitis (HP) caused by inhaling humidifier vapor contaminated with bacteria, fungi, or endotoxins that have developed in stored water in the humidifier. Ultrasonic humidifiers are one type of humidifier. In Japan, they are increasingly used during winter to prevent dryness in the home and indoor environment. Ando et al. showed that humidifier lung accounts for only 4.3% of all HP cases in Japan [1,2]. However, in recent years, with the widespread use of ultrasonic humidifiers, the number of reported cases of ultrasonic humidifier lung is increasing [3,4]. The characteristic high-resolution computed tomography (HRCT) scan findings of HP were lung infiltration (i.e., ground-glass opacity, mosaic attenuation) plus at least 1 HRCT abnormality indicative of small airway disease, including ill-defined, small (<5 mm) centrilobular nodules on inspiratory images [5]. However, in recent years, the imaging findings of humidifier lung may not match the typical imaging findings of HP because of the high frequency of bilateral frosted shadows and consolidations and the low frequency of lobular central frosted lesions [6].

The reversed halo sign (RHS) is described as a focal rounded area of ground-glass opacity surrounded by a more or less complete ring of consolidation [7]. RHS was initially reported as a finding of cryptogenic organizing pneumonia (COP). Further, it is considered a specific CT scan finding of this disease [8], which accounts for 12%-19% of COP cases [9]. Recently, RHS has been observed in different diseases other than COP [10,11]. Infectious diseases with RHS include fungal infections (such as paracoccidioidomycosis [12,13], pulmonary mucormycosis [14,15], and invasive pulmonary aspergillosis [14,16]), pulmonary tuberculosis [17,18], pneumocystis pneumonia [19], and coronavirus disease 2019 [20]. Noninfectious diseases with RHS other than COP [10,11] include sarcoidosis [21,22], drug-induced pneumonitis [23], granulomatosis with polyangiitis [24], pulmonary infarction [25], and bronchoalveolar carcinoma [26]. However, there have been no reported cases of humidifier lung with RHS. Herein, we report a case of ultrasonic humidifier lung with RHS.

Case report

An 82-year-old Japanese male patient was treated with darolutamide, an oral androgen receptor inhibitor, for prostate cancer during winter. On the 43rd day of treatment, the patient presented with appetite loss and fatigue and subsequently developed dry cough. On the 48th day of treatment, he experienced moving difficulties and visited our hospital. He had no smoking history. He had a medical history of hypertension and osteoporosis and was taking antihypertensive drugs and bisphosphonates.

Upon admission, he had no fever. His pulse rate was 96 beats/min, and his transcutaneous arterial oxygen saturation (SpO_2) at room air was 92%. Inspiratory crackles were auscultated at the base of the lungs on both sides. The patient's white blood cell (WBC) count was 17400/μL (normal value: 3300–8600/μL) with a neutrophil count of 82.7%, and his C-reactive protein (CRP) level was 16.88 mg/dL (normal value: ≤0.14 mg/dL). Chest radiography revealed infiltrative shadows and ground-glass opacities on both sides, predominantly on the distal area. HRCT revealed bilateral extensive nonsegmental ground-glass opacities in the peripheral regions and extensive areas of ground-glass opacity with a circumferential halo of consolidation indicating RHS (Fig. 1).

After hospitalization, darolutamide was discontinued because drug-induced organizing pneumonitis was suspected. Treatment with ampicillin/sulbactam was started for bacterial pneumonia. After 9 days of antibiotic treatment, loss of appetite, fatigue, and chest radiography abnormality improved. Hence, the patient was discharged from the hospital. However, he developed slight fever, cough, and dyspnea and revisited the hospital 3 days after discharge. HRCT again showed extensive nonsegmental ground-glass opacities and RHS in the peripheral regions on both sides. The patient was then admitted urgently to the hospital. After starting treatment with tazobactam/piperacillin, fever, cough, dyspnea, and chest radiography shadows improved. The patient was discharged from the hospital after 8 days of antibiotic treatment. The patient's Krebs von den Lungen 6 level was 376 U/mL (normal value: ≤500 U/mL). Various autoantibody blood tests were performed to investigate the cause of secondary organizing pneumonia (OP). However, no abnormalities were observed. One day after hospital discharge, the patient experienced fever and dyspnea and visited the hospital again. His SpO_2 level at room air was 89%, and HRCT again showed extensive nonsegmental ground-glass opacities and RHS in the peripheral regions on both sides (Fig. 2A). The patient was again admitted urgently to the hospital.

Due to pneumonia recurrence, the patient was hospitalized twice immediately after being discharged from the hospital. Due to his clinical course, HP was suspected, and a detailed medical history was obtained. Results showed that the patient had purchased an ultrasonic humidifier 2 months before he initially contracted pneumonia. Further, he used the humidifier at home every after hospital discharge. After admission, the patient was followed-up without the use of antibiotics, and symptoms, respiratory failure, and CT scan shadows immediately improved (Fig. 2B). Bronchoscopy was performed after 5 days of hospitalization, and bronchoalveolar lavage (BAL) showed an elevated cell count of 3.94×10^5/mL

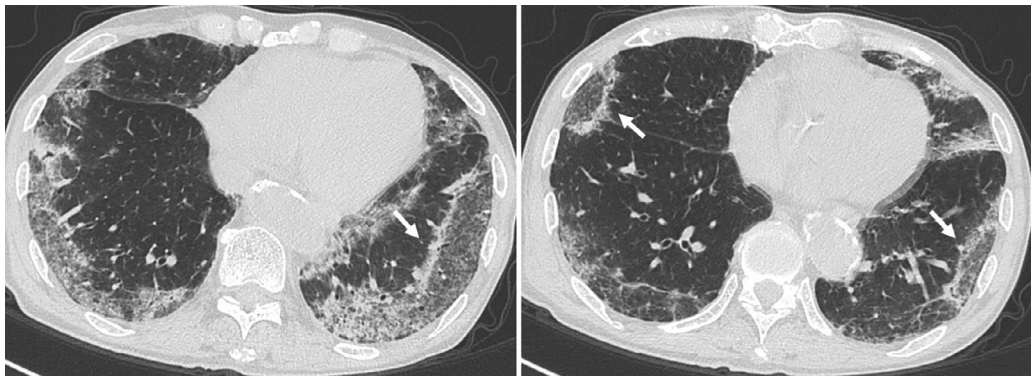

Fig. 1 – High-resolution chest computed tomography scan during the initial hospitalization. The patient presented with nonsegmental ground-glass opacities in the peripheral regions on both sides and extensive areas of ground-glass opacity with a circumferential halo of consolidation, indicating a reversed halo sign (arrows).

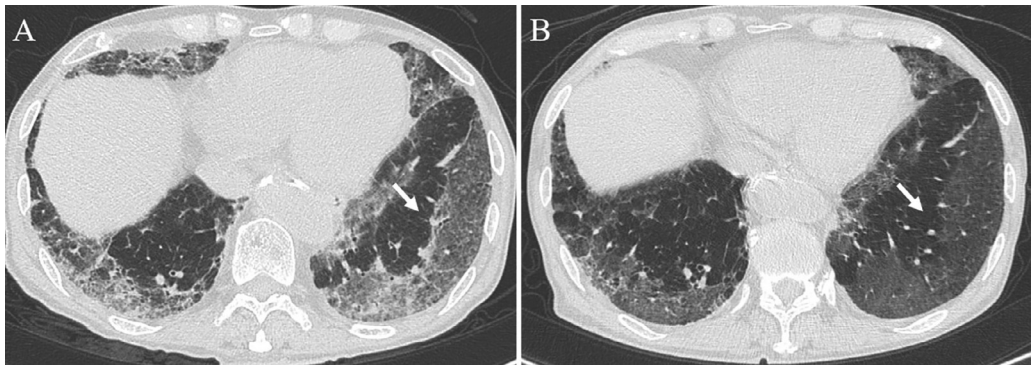

Fig. 2 – High-resolution chest computed tomography scan during the third hospitalization. Upon admission (A), the patient presented with nonsegmental ground-glass opacities in the peripheral regions on both sides, and extensive areas of ground-glass opacity with a circumferential halo of consolidation, indicating a reversed halo sign (RHS) (arrow). On the fifth day of hospitalization (B), ground-glass opacities and RHS improved (arrow).

with the following differential counts: lymphocyte, 47%; neutrophil, 13%; and eosinophil, 23%. The T-cell $CD4^+/CD8^+$ ratio was 0.82. Transbronchial lung biopsy revealed slight alveolitis and intra-alveolar fibrosis, which are pathological findings of organizing pneumonia. However, granuloma was not identified (Fig. 3). BAL cytology and culture confirmed the presence of *methicillin-resistant Staphylococcus aureus* and *Candida albicans*. As humidifier lung was suspected, the provocation test was performed using an ultrasonic humidifier that used at the patient's home. Approximately 5 hours after the start of the test, he developed cough, dyspnea, and fever (38.7°C), and his SpO_2 level decreased from 98% to 87%. The blood tests showed an increased WBC count (17800/μL) and CRP level (0.62 mg/dL). Chest radiography showed worsening of ground-glass opacities in both lung fields. Therefore, the patient was diagnosed with humidifier lung [27]. The tests for precipitated antibody reactions using serum samples or humidifier water were not performed. Non-glucose-fermenting gram-negative bacilli, glucose-fermenting gram-negative bacilli, γ-Streptococcus, Micrococcus species, and *Candida glabrata* were detected in the water from the humidifier. After hospital discharge, the patient avoided the use of the causative humidifier. Then, darolutamide treatment was resumed, and the patient did not present with pneumonia recurrence.

Discussion

There are no reports of cases on humidifier lungs with RHS. Upon the initial diagnosis, drug-induced organizing pneumonia was primarily considered as the patient had a history of darolutamide treatment and RHS was observed on imaging. Hence, in our case, it took time to make a definitive diagnosis of humidifier lung. HP is an allergic disease caused by repeated inhalation of organic or inorganic dust and sensitization to these antigens. In recent years, household ultrasonic humidifiers generating a low-temperature steam have become popular, and reports about humidifier lung have become more common [6]. HP is accompanied by chronicity and fibrosis in response to long-term antigen exposure. Therefore, early diagnosis and antigen avoidance are important for treatment, and radiological differential diagnosis plays an important role. In general, HP is not a representative disease with RHS. RHS in a farmer's lung, which is a type of HP, has been observed [28].

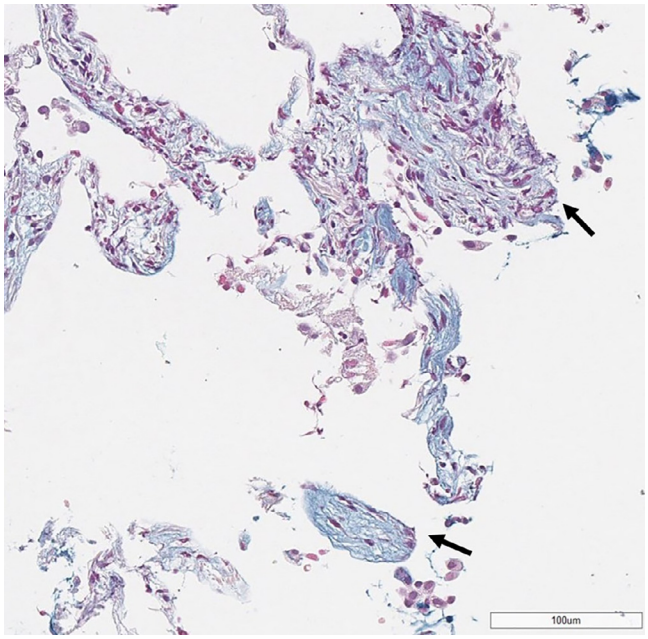

Fig. 3 – Alveolitis and intra-alveolar fibrosis were observed on the transbronchial lung biopsy specimen (arrows), and no granulation species could be identified (×20).

However, there is no report about RHS in patients with humidifier lung.

In the current case, the radiological CT scan findings were RHS, bilateral extensive nonsegmental ground-glass opacities, and consolidation in the peripheral regions. However, there were no findings indicative of bronchiolar lesions such as centrilobular nodules. To the best of our knowledge, there are limited reports on the radiological features of humidifier lung. Sakamoto et al. reported a comparison of ultrasonic humidifier lungs with summer-type HP, which is a common type of HP in Japan [6]. In this report, the main CT scan findings of summer-type HP were diffuse ground-glass opacity and centrilobular nodule. However, the main findings on ultrasound humidifier lung CT scan were ground-glass opacity and peribronchovascular or subpleural nonsegmental consolidation, which is rare in summer-type HP. The characteristics of this ultrasonic humidifier lung imaging finding were consistent with those of our case. In addition, in another report of a patient with humidified lung who was diagnosed with OP based on pathological findings on bronchoscopy, as in our case, granuloma was not observed. Moreover, the only findings were intracavitary organization and alveolitis. Based on the provocation test, a diagnosis of humidifier lung was made [29]. Further, in a study examining the BAL fluid of secondary OP, changes in the macrophage/lymphocyte ratio and increased neutrophil, eosinophil, and mast cell counts were observed [30], which is consistent with the BAL findings in our case. Therefore, radiologically and pathologically, this case can be considered as secondary OP in the humidifier lung.

In a previous report involving 79 patients with RHS, 11 patients presented with secondary OP; RHS that appears late during the disease can be associated with secondary OP [11]. Therefore, humidifier lungs may also present with RHS during secondary OP. In addition, the characteristics of humidifier lungs may differ based on the type of humidifier. In our case, the humidifier used was an ultrasonic humidifier. The incidence of humidifier lung caused by ultrasonic humidifiers is higher than that attributed to other types of humidifiers [31]. The reasons are as follows: First, the water in the ultrasonic humidifier is not heated to sterilizing temperatures, and fungi can easily grow in the water in the humidifier. Second, the particles generated by ultrasonic humidifiers are small at 0.5-3 μm, and may easily reach the peripheral airways and lung parenchyma. Third, the generator itself, towers, and nozzles of ultrasonic humidifiers are generally difficult to clean. Finally, in Japan, gram-negative bacilli, fungi, and acid-fast bacteria have been identified as the causative agents of ultrasonic humidifier lung [31,32]. Inhaling the endotoxins produced by these agents increases the number of neutrophils and lymphocytes in the BAL and peripheral blood. Moreover, it promotes the production of inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), resulting in various acute lung injuries, including OP pattern [33,34].

In our case, HP was evaluated with moderate confidence according to the 2020 ATS/JRS/ALAT diagnostic criteria [5]. In the latest guidelines, the diagnostic criteria include centrilobular opacities, a radiological item, and granuloma, a pathological item. In humidifier lungs, these characteristic findings of HP may be less common in the clinical setting and may be underestimated. Therefore, it can be useful to gather cases of humidifier lung and establish diagnostic criteria specific to humidifier lung.

Conclusion

Herein, we report a rare case of ultrasonic humidifier lung with RHS. Humidifier lung is associated with OP pattern due to prominent lung damage rather than the typical HP accompanied by bronchiolar lesions. RHS is observed in various diseases. Hence, ultrasonic humidifier lung should be considered as a differential diagnosis in patients with RHS, and a detailed medical history must be obtained.

Patient consent

Informed consent was obtained from the patient, and it is available upon request.

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